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NOVEMBER 1950
VOLUME 64 NUMBER 5

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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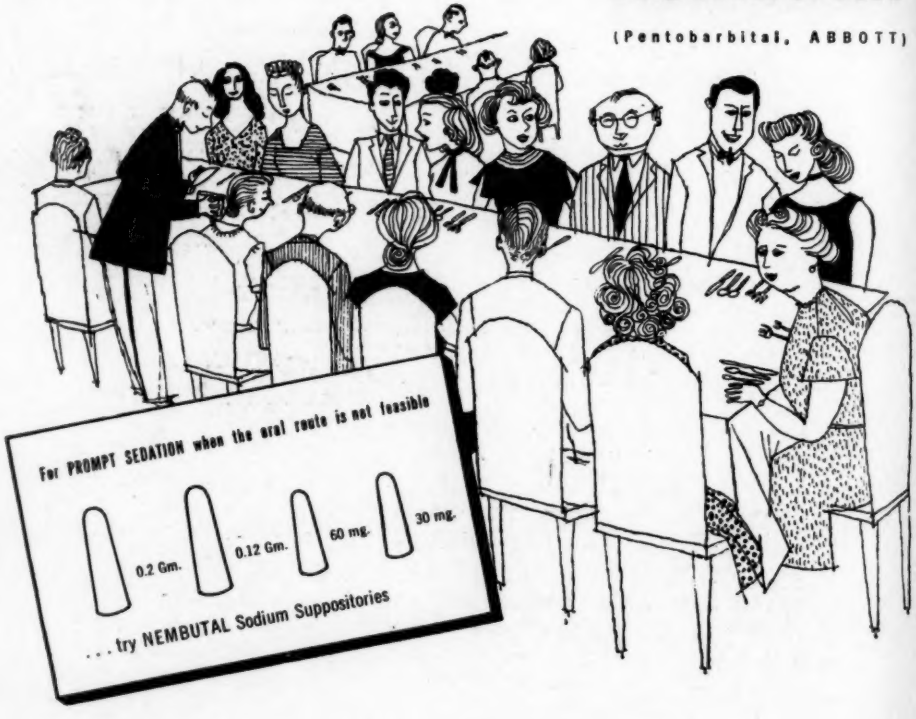

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 64 NOVEMBER 1950 NUMBER 5

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PAIN THRESHOLD STUDIES ON PARAPLEGIC PATIENTS

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ACCURATE interpretation of pain in the presence of paraplegia presents a challenging problem. Essentially two types of pain occur when the spinal cord has been severely traumatized: root pain and vascular pain.[1] The latter appears intermittently with varying degrees of severity in almost all paraplegic patients. Surgical therapy for this type of pain has been ineffectual, although at first sympathectomy was viewed with hopefulness. On the other hand, it is desirable to treat the root type of pain surgically and early if addiction to drug and alcohol is to be prevented and proper rehabilitation of the patient is to be achieved. Experiences at this clinic [2] indicate that lateral spinothalamic tractotomy is the operative treatment of choice in the presence of unquestioned root pain below the fifth thoracic dermatome. It is the purpose of this communication to present evidence fortifying the value of threshold studies and their application in molding the indications for surgical intervention in the treatment of pain in paraplegic patients.

METHOD AND MATERIAL

Case Material.—A. The main threshholds for perception of pain and for reaction to pain were determined on 100 quadriplegic and paraplegic patients

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Freeman, L. W.: Treatment of Paraplegia Resulting from Trauma to the Spinal Cord, J. A. M. A. **140**:949-958 (July 16) 1944; **140**:1015-1022 (July 23) 1949.

2. Meirowsky, A. M.: Unpublished data. De Saussure, R. L., Jr.: Lateral Spinothalamic Tractotomy for the Relief of Pain in Cauda Equina Injury, Arch. Neurol. & Psychiat., this issue, p. 708.

who were hospitalized for the purpose of rehabilitation and who did not present a particular pain problem. Ten of the patients of this group underwent psychometric studies.

B. The thresholds for perception of pain and for reaction to pain were determined on three patients with traumatic lesions of the cauda equina who were suffering from severe root pain. These three patients ultimately underwent lateral spinothalamic tractotomy and were studied before and after operation. Psychometric studies were also carried out on these three patients before and after operation.

Technic of Threshold Studies.—The Hardy-Wolff pain threshold [3] apparatus was employed throughout this study in order to determine quantitatively the thresholds for perception of pain and for reaction to pain. A standardized radiometer was used to check the instrument's calibration at frequent intervals. The source of stimulation was heat from a calibrated 500 watt electric bulb, which was focused by a lens on an india ink spot on the patient's forehead. Exposure was made for a period of three seconds. Readings were expressed in millicalories per second per square centimeter.

In studying the threshold for reaction to pain, the pulse rate was ultimately used as indicator because it was found to be the most sensitive clinical end point which gave a constant and reliable reaction to pain. Dilation of the pupil, goose pimples, clenching of the teeth and changes in blood pressure and respiratory rate appeared to be unreliable factors and usually occurred subsequent to the change in the pulse rate. An increase of 10 or more per minute in the pulse rate was interpreted as a measure of the patient's reaction to a painful stimulus, a component of the "alarm" reaction. A simultaneous reading of the pain apparatus was recorded, and this was taken as the pain reaction threshold, expressed in millicalories per second per square centimeter.

The pain preception threshold was recorded as the lowest stimulus necessary to elicit a sensation of pricking or sharp stabbing. In order that the data should be as objective as possible, the threshold for perception of pain was obtained as described by Chapman.[4]

For purposes of standardization, all tests were made by the same examiner (L. A. H.). The stimulus was always increased in increments of 5 millicalories per second per square centimeter. Between each exposure a rest period of two minutes was allowed to elapse. Each patient was subjected to four or more tests at different time intervals.

Psychometric Studies.—Ten patients of the control group were examined psychometrically (table 1). The three patients with a problem of cauda equina pain were examined before and after operation, in an attempt to establish a personality adjustment differential. Certain Rorschach signs established by Harrower-Erickson [5] were used. The control group made an average score of 9.5 (range 4.0 to 16.5). Average adjustment is postulated by the score of 9.5. Degrees of adjustment below and above this score suggest better and poorer than average adjustment, respectively.

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3. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain. New Method for Measuring Pain Threshold: Observations on Spatial Summation of Pain, J. Clin. Investigation **19**:649-657 (July) 1940.

4. Chapman, W. P.: Measurements of Pain Sensitivity in Normal Control Subjects and in Psychoneurotic Patients, Psychosom. Med. **6**:252-257 (July) 1944.

5. Harrower-Erickson, M. R.: The Values and Limitations of the So-Called "Neurotic Signs," Rorschach Res. Exch. **6**:10-14, 1942.

TABLE 1.—*Pain Thresholds* in Control Group of Patients, Including Ten Patients Who Underwent Psychometric Evaluation*

Case	Level of Lesion	Presence of Paralysis, Years	Pain Perception Threshold	Pain Reaction Threshold	Psychometric Scale Reading
1	C 5	2.00	226 ± 4	120-144	5.0
2	C 6	2.33	234 ± 2	120-135	4.0
3	C 8	3.00	230 ± 2	112-150	14.0
4	C 6	3.50	230 ± 4	120-146	12.0
5	T 8	5.50	230 ± 2	110-130	4.5
6	T 8	4.33	230 ± 2	124-150	6.0
7	T 9	1.50	228 ± 2	110-150	16.5
8	T 9	4.33	234 ± 2	120-140	7.0
9	L 1	2.00	226 ± 4	124-154	11.0
10	L 2	2.33	224 ± 2	110-155	15.5
11	C 5	5.00	230 ± 6	120-140	..
12	C 5	5.33	234 ± 4	122-140	..
13	C 7	1.00	230 ± 2	120-146	..
14	C 7	3.00	236 ± 6	115-140	..
15	C 7	1.33	228 ± 4	124-136	..
16	C 5	3.25	226 ± 4	114-146	..
17	C 7	1.25	228 ± 2	114-136	..
18	C 6	1.25	228 ± 6	114-148	..
19	C 8	1.00	230 ± 2	118-146	..
20	C 7	1.50	228 ± 4	124-138	..
21	C 8	1.50	230 ± 4	116-138	..
22	C 8	6.00	232 ± 4	120-148	..
23	C 5	1.00	234 ± 4	128-148	..
24	C 5	4.25	230 ± 4	128-144	..
25	C 7	5.00	238 ± 2	126-140	..
26	C 5	3.00	224 ± 4	110-134	..
27	C 7	5.25	230 ± 2	120-148	..
28	C 5	2.50	226 ± 4	110-130	..
29	T 5	2.25	234 ± 4	110-128	..
30	T 6	9.00	220 ± 2	112-120	..
31	T 4	5.66	226 ± 4	114-130	..
32	T 12	3.50	228 ± 2	120-130	..
33	T 8	1.25	226 ± 4	118-130	..
34	T 4	1.00	226 ± 4	116-130	..
35	T 11	2.50	224 ± 4	110-150	..
36	T 6	2.00	230 ± 4	118-140	..
37	T 8	1.25	230 ± 4	110-120	..
38	T 11	1.33	225 ± 5	124-138	..
39	T 6	3.00	234 ± 4	118-150	..
40	T 11	1.66	230 ± 4	118-130	..
41	T 5	1.33	226 ± 4	120-130	..
42	T 4	5.33	234 ± 4	128-142	..
43	T 11	2.00	230 ± 4	120-136	..
44	T 4	7.50	236 ± 2	134-148	..
45	T 7	5.00	230 ± 4	126-136	..
46	T 7	2.00	226 ± 6	118-136	..
47	T 10	1.00	228 ± 4	120-134	..
48	T 12	3.50	234 ± 4	126-138	..
49	T 10	2.60	232 ± 2	120-146	..
50	T 6	4.50	230 ± 2	122-140	..

* Thresholds for perception of pain and reaction to pain are expressed in millicalories per second per square centimeter.

TABLE 1.—*Pain Thresholds* in Control Group of Patients, Including Ten Patients Who Underwent Psychometric Evaluation—Continued*

Case	Level of Lesion	Presence of Paralysis, Years	Pain Perception Threshold	Pain Reaction Threshold	Psychometric Scale Reading
51	T 6	5.50	234 ± 4	130-150	..
52	T 7	6.33	230 ± 4	126-148	..
53	T 8	32.00	230 ± 2	120-150	..
54	T 8	5.25	232 ± 2	115-150	..
55	T 8	2.50	232 ± 2	126-146	..
56	T 7	2.33	230 ± 2	120-140	..
57	T 11	1.00	234 ± 4	122-146	..
58	T 11	4.33	236 ± 4	115-130	..
59	T 8	2.25	228 ± 2	120-134	..
60	T 11	1.00	230 ± 4	120-155	..
61	T 12	3.00	230 ± 4	120-134	..
62	T 12	4.00	224 ± 4	116-140	..
63	T 1	2.50	226 ± 2	118-138	..
64	T 10	2.50	230 ± 2	130-144	..
65	T 8	14.00	232 ± 2	120-140	..
66	T 8	3.50	224 ± 4	126-148	..
67	T 6	3.00	236 ± 2	115-130	..
68	T 12	1.25	230 ± 2	120-148	..
69	T 8	3.25	226 ± 4	120-140	..
70	T 9	3.00	230 ± 4	112-138	..
71	T 12	4.25	224 ± 2	120-138	..
72	T 6	5.00	234 ± 2	120-155	..
73	T 8	1.25	232 ± 2	118-144	..
74	T 3	5.00	230 ± 2	118-140	..
75	T 5	5.00	228 ± 2	126-150	..
76	T 4	1.50	234 ± 2	128-138	..
77	T 1	5.50	224 ± 2	118-146	..
78	T 8	1.50	228 ± 2	122-142	..
79	T 11	5.33	236 ± 4	124-138	..
80	T 11	6.50	226 ± 2	114-134	..
81	T 12	1.33	230 ± 2	120-150	..
82	T 6	5.00	226 ± 4	128-144	..
83	T 8	1.50	230 ± 2	110-140	..
84	T 6	4.00	228 ± 2	134-144	..
85	T 4	4.50	236 ± 4	122-136	..
86	T 11	1.66	226 ± 4	110-138	..
87	T 10	2.50	230 ± 2	118-140	..
88	T 6	2.66	226 ± 4	110-150	..
89	T 6	1.66	230 ± 4	124-134	..
90	L 1	1.00	236 ± 4	120-140	..
91	L 4	1.50	228 ± 4	120-134	..
92	L 1	1.00	230 ± 2	120-140	..
93	L 5	6.00	234 ± 2	120-146	..
94	L 1	22.00	228 ± 4	120-144	..
95	L 3	3.25	230 ± 2	120-134	..
96	L 1	4.50	230 ± 4	118-150	..
97	L 1	2.00	232 ± 4	130-150	..
98	L 4	1.33	238 ± 2	120-138	..
99	L 4	1.00	226 ± 4	136-154	..
100	L 1	1.25	230 ± 4	126-154	..

* Thresholds for perception of pain and reaction to pain are expressed in millicalories per second per square centimeter.

RESULTS

Control Group.—One hundred paraplegic and quadriplegic patients, not presenting a particular pain problem, were tested with the Hardy-Wolff machine (table 1). The mean average threshold for perception of pain was found to be 230 ± 10 millicalories per second per square centimeter. The extreme range of thresholds for reaction to pain was 110 to 155 millicalories, with the readings for the majority of patients falling into the range of 120 to 140 millicalories per second per square centimeter. The threshold for reaction to pain was found to follow the pattern described by Wolff [6] but remained within the aforementioned boundaries.

Patients with Intractable Pain.—Three patients with intractable root pain, subsequent to severe trauma to the cauda equina which resulted in paraplegia, were selected for studies of the pain threshold and for

TABLE 2.—*Pain Thresholds* and Psychometric Readings for Three Patients Who Had Undergone Bilateral Spinothalamic Tractotomy for Intractable Cauda Equina Pain*

Case	Level of Lesion	Presence of Paralysis, in Years	Pain Perception Threshold		Pain Reaction Threshold		Psychometric Scale Reading	
			Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
H. C.	L 2	1.25	270 ± 20	234 ± 2	280-315	118-130	9.0	5.0
R. M.	L 2	1.25	265 ± 5	234 ± 4	130-228	114-130	9.5	4.0
J. W.	L 3, 4	1.00	250 ± 10	230 ± 2	180-240	118-130	6.5	6.5

* Thresholds for perception of pain and reaction to pain are expressed in millicalories per second per square centimeter.

psychometric studies. In the presence of intractable pain, prior to lateral spinothalamic tractotomy, all three patients showed a distinct increase in the threshold for perception of pain and an even more remarkable increase in the threshold for reaction to pain. Lateral spinothalamic tractotomy in all three patients resulted in complete relief from pain. Threshold studies subsequent to the tractotomy revealed a striking return of perception and reaction thresholds to a normal range (table 2).

Psychometric Studies.—The preoperative psychometric scale ratings for two of the three patients were approximately the score for average adjustment, while the third was somewhat better than average. After operation the first two patients improved their scores appreciably in the direction of better than average adjustment, while the third patient

6. (*a*) Wolff, H. G.; Hardy, J. D., and Goodell, H.: Studies on Pain: Measurement of Effect of Ethyl Alcohol on Pain Threshold and an "Alarm" Reaction, J. Pharmacol. & Exper. Therap. **75**:38-49 (May) 1942. (*b*) Schumacher, G. A.; Goodell, H.; Hardy, J. D., and Wolff, H. G.: Uniformity of Pain Threshold in Man, Science **92**:110-112 (Aug. 2) 1940.

maintained the same level of adjustment. These results seem to indicate that the relief of pain has a positive bearing on the improvement of personality adjustment.

COMMENT

The results of this study suggest that the threshold for perception of pain in patients with long-standing paraplegia and quadriplegia is not at variance with that found in the nonparaplegic population, as studied by Wolff and his group.[7] The instability of the threshold for reaction to pain also is the same as that observed by Wolff.[6] While the threshold for reaction to pain has been found to be lower in our group than that reported from other clinics,[8] one would hardly be justified in concluding that this lowered threshold for reaction to pain is specific for people enduring long-standing paraplegia, although this deduction has to be considered. As already mentioned, we have found the pulse rate to be an earlier and more constant indicator than any of the other reactions which have been used by various examiners.[8] This different indicator may be responsible for the lower readings recorded in studying the reaction to pain in paraplegic patients.

The persistent increase in the thresholds for perception and for reaction to pain in patients with intractable pain has been most striking. The return to normal of the threshold ranges for perception and for reaction to pain following relief from pain by lateral spinothalamic tractotomy indicates that the increased threshold in the presence of intractable pain is a direct sequela of the long-standing endurance of pain. We are therefore inclined to believe that threshold studies can readily and reliably be used in establishing the indications for surgical intervention in the presence of intractable pain.

SUMMARY

The thresholds for perception of pain and for reaction to pain have been determined on 100 paraplegic patients who did not present a particular pain problem. The mean average of the threshold for perception of pain was found to be 230 ± 10 millicalories per second per square centimeter. When the pulse rate was employed as the indicator, the threshold for reaction to pain fell within an average range of 110 to 155 millicalories per second per square centimeter.

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7. Hardy, Wolff and Goodell.[3] Schumacher, Goodell, Hardy and Wolff.[6b]

8. Hardy, Wolff and Goodell.[3] Schilling, R. F., and Musser, M. J.: Pain Reaction Thresholds in Psychoneurotic Patients, Am. J. M. Sc. **215**:195-197 (Feb.) 1948. Chapman, W. P.; Cohen, M. E., and Cobb, S.: Measurements Related to Pain in Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome: Levels of Heat Stimulus Perceived as Painful and Producing Wince and Withdrawal Reactions, J. Clin. Investigation **25**:890-896 (Nov.) 1946.

Three paraplegic patients with intractable root pain subsequent to injury to the cauda equina were studied before and after operation, as in the control group. Prior to surgical intervention for relief of pain, all three patients showed distinctly elevated thresholds for perception and for reaction to pain. After relief from pain by the lateral spinothalamic tractotomy, the thresholds for perception and for reaction to pain returned to a normal range in all three patients.

It is suggested that threshold studies may be profitably employed in establishing the indication for surgical intervention in the presence of intractable pain.

NASAL GLIOMA

Two Cases with Recurrence

BOYD K. BLACK, M.D.*
AND
DAVID E. SMITH, M.D.
ST. LOUIS

TUMORS in the region of the nose which are composed of glial tissue and occasionally contain neuronal elements have been reported by various authors. These lesions have usually been congenital and have occurred extranasally at the root of the nose, intranasally or, in a few instances, at both sites. That there is no clear concept of the nature of these tumors is indicated by the varied terminology under which essentially similar cases have been reported. The commonest name applied is nasal glioma, but other terms are glioma (astrocytoma),[1] fibroglioma,[2] encephalochoristoma naso-frontalis,[3] encephaloma[4] and encephalocele.[5] It is generally agreed that these lesions are of a benign character, but there has been little evidence to indicate whether they have the properties of growth characteristic of a benign neoplasm or whether they are simply malformations. It is the purpose of this paper to report two cases of such lesions in which there was a recurrence of the tumor at the site of removal. The cases reported in the literature are reviewed to provide an understanding of the nosology of these tumors.

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From the Departments of Pathology and Surgery (Surgical Pathology), Washington University School of Medicine.

1. Schwartz, A. A., and Isaacs, H. J.: Glioma (Astrocytoma) of the Nares, Arch. Otolaryng. **34**:838 (Oct.) 1941.

2. Rocher, H. L., and Anglade: Les fibrogliomes de la région nasale, Rev. de chir. **62**:147, 1924.

3. Zettergren, L.: On the So-Called Nasal Gliomas, Acta path. et microbiol. Scandinav. **25**:672, 1948.

4. Berger, P.: Considérations sur l'orgine, le mode de développement et le traitement de certaines encéphalocèles, Rev. de chir. **10**:269, 1890.

5. Comninos, O.: Encéphalocèle à structure mixte fibro-gliomateuse, Arch. d'opht. **31**:177, 1911.

The first lesion of this nature described in the literature was reported in 1900 by Schmidt,[6] who referred to it as a glioma. The author considered the possibilities of this tumor originating either as a teratoma or as an encephalocele, still the two most obvious explanations for the occurrence of glial tissue in an abnormal site. Although the occurrence of dermoid cysts of the forehead is well recognized, it is unusual for such cysts to contain complex teratomatous elements.[7] Furthermore, as Schmidt observed in his discussion, the unilateral differentiation of a teratoma solely into tissue of neuroectodermal derivation is not a recognized phenomenon. This point is substantiated by more modern studies of teratomas.[8] Authors since Schmidt have consequently rejected the possibility of the development of the nasal glioma from teratoma, and none have reported cases in which an admixture of epithelial or other recognizably teratomatous elements occurred.

Encephaloceles are distinguished from the nasal gliomas with greater difficulty. The two lesions may occur in similar sites, but the ultimate criterion on which they have been differentiated in this paper is the presence of a connection with the subarachnoid space or the cerebral ventricles in the encephalocele and the absence of such a connection in the nasal glioma. The other gross and histological features of these two lesions may be similar.

REPORT OF CASES

CASE 1.—J. D. D., a white infant boy, was born at term after a normal gestation. A small tumor was present at birth on the bridge of the nose to the left of the midline and was said to have increased slowly in size during the following months. At the age of 4 months the child was examined and described as normal except for the tumor, which was firm, round and 1 cm. in diameter. It was freely movable on the bridge of the nose, adherent to the overlying skin and nonfluctuant. The tumor was then removed by sharp dissection. Close attention was paid to the base, as the operator suspected it might be a meningocele, but no pedicle was found. The postoperative course was uneventful.

Two years and four months later the patient's mother noticed the appearance of a small lump in the operative scar; this tumor enlarged to a diameter of 5 mm. in the following eight months. It was firm and not fixed to the overlying scar or the nasal bones. The examiner noted that the nasal portions of the maxillary bones were separated and there was some deficiency of the anterior superior nasal cartilages. Roentgenographic examination of the underlying bones was unsatisfactory. At operation the recurrent tumor was removed and dissection carried as deep as the bare bone, without discovery of any process extending from the tumor. The total volume of tumor removed was approximately 4 cc. The patient's recovery was uneventful.

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6. Schmidt, M. B.: Über seltene Spaltbildungen im Bereiche des mittleren Stirnfortsatzes, Virchows Arch. f. path. Anat. **162**:340, 1900.

7. Schmidtmann, M., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1928, vol. 3, pt. 1, p. 248.

8. Willis, R. A.: Pathology of Tumours, St. Louis, C. V. Mosby Company, 1948, p. 940.

In sections of the excised tumor (fig. 1) there were broad bands and islands of glial tissue separated by thick columns and septums of coarse collagenous fibers. The glial islands were composed entirely of cells with the appearance of astrocytes. The stroma was the finely fibrillary matrix typically present in the central nervous system. Most of the cells had ovoid, moderately dense nuclei and little visible cytoplasm; but about one third were atypical forms, varying from cells with large, prominent, eosinophilic cytoplasm and dark, pyknotic nuclei to forms with large, ovoid, rarefied nuclei and little visible cytoplasm. The latter often had lobulated nuclei and a distinct central lump of chromatin, but true nucleoli were not present. There were also scattered cells that had two or three nuclei. No mitotic figures were present, and none of the cells had the appearance of ganglion cells. In

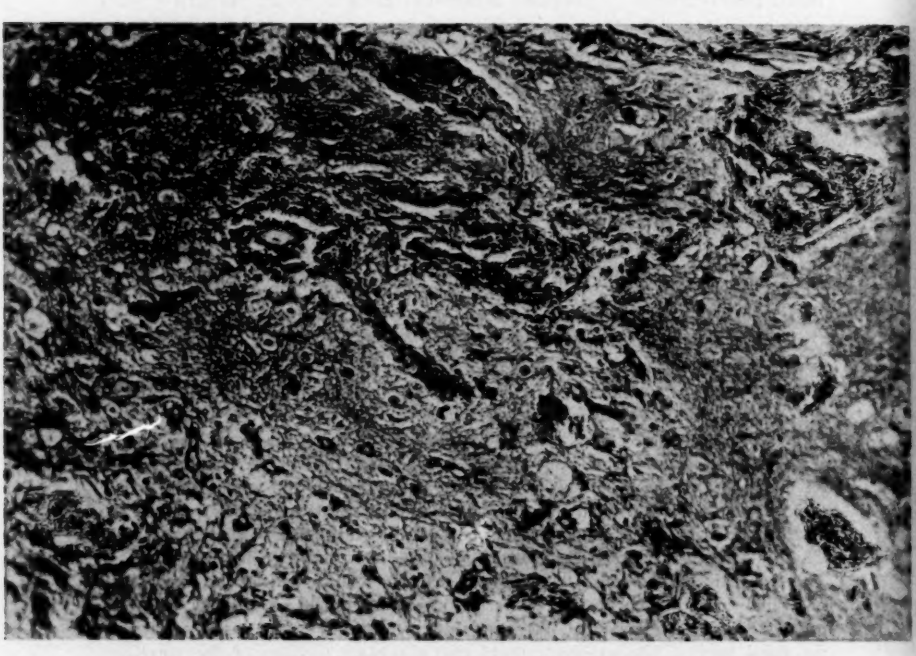

Fig. 1 (case 1).—Broad islands of glia in a fibrous stroma from a section of tumor removed at the original operation. Phosphotungstic acid–hematoxylin stain; × 230.

preparations with Mallory's phosphotungstic acid–hematoxylin stain the matrix fibrils of the glial islands stained a sharp blue, in contrast with the coarse fibers of the septums, which stained in the red or violet manner of collagen and fibroglia. The fibrous septums contained a moderate number of thin-walled blood vessels, and at the junction with the glial tissue was a narrow zone of lacy, vacuolated tissue spaces, in the interstices of which was a light basophilic precipitate. Sections impregnated by the Perdrau method showed abundant reticulin in the septums and occasional fibers about small blood vessels in the glial islands. The Gros-Bielschowsky method impregnated no structures within the glial islands which resembled neurofibrils, and the cresyl violet stain added no further information.

In sections of the recurrent tumor (fig. 2) were small islands of typical glial tissue, such as were present in the original tumor, but the fibrous septums were much larger and were composed of coarse, almost hyaline fibers. Between these septums were bands of tissue composed of irregular bundles of coarse fibrils which stained in the manner of collagen with the Mallory phosphotungstic acid–hematoxylin method and intimately admixed blue fibrils which were slightly thicker than the usual neuroglia but were not intracellular in the manner of fibroglia. Associated with the blue fibrils were cells with round or ovoid, irregular nuclei and the appearance of astrocytes. This mixed tissue comprised about one-half the area of the section, and the fibrous septums the other half. Because the tumor was fixed in Bouin's solution, the Perdrau and Gros-Bielschowsky impregnations

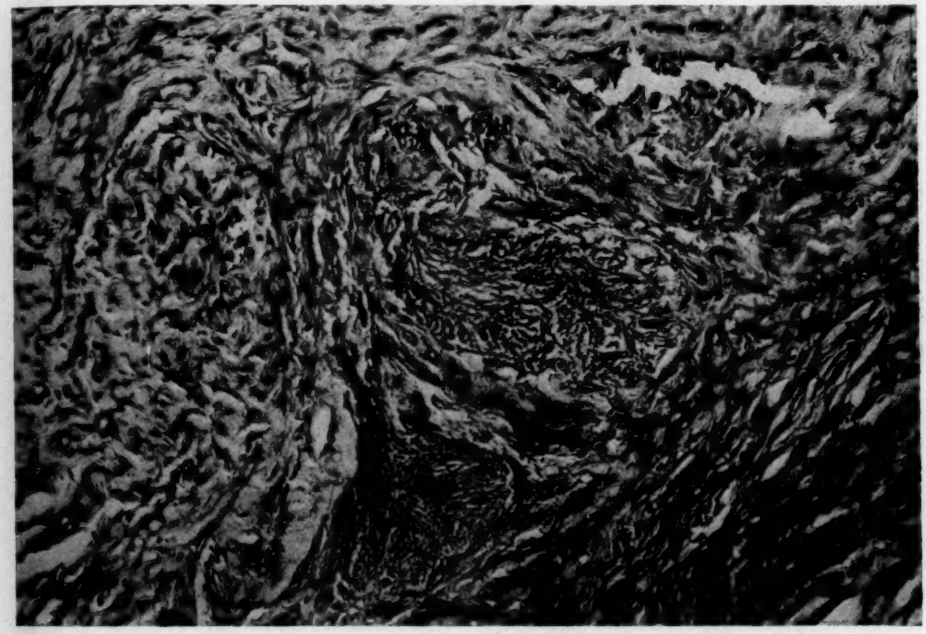

Fig. 2 (case 1).—Small island of glia in a dense collagenous stroma in the recurrent tumor. Phosphotungstic acid–hematoxylin stain × 230.

were not satisfactory, and the cresyl violet stained no cells that resembled ganglion cells. Two small foci of foreign body reaction were present on a margin of one section.

CASE 2.—E. W. P.,[9] a white infant boy, was born at term after a normal gestation. Except for a tumor about 12 mm. in diameter beneath the skin of the left side of the nose, the child was of normal appearance. At the age of 6 days the

9. The early history of this case was reported in detail by Dr. J. H. Hill and is summarized here for convenience of reference. Dr. Hill furnished his reports to us and allowed us to inspect preparations from the original tumor. (Hill, J. H.: Arch. Path. **48**:183 [Aug.] 1949.)

tumor was removed by blunt dissection, and the base of the wound was fulgurated. No pedicle extending from the tumor was discovered. The wound healed promptly.

One year later a small nodule of growing tissue was discovered on the lateral side of the operative scar. Within six weeks it had enlarged until it was 1.5 in length and 2 cm. in breadth. The mass was of irregular contour and soft, nontender and spongy. There were no abnormalities of the head or eyes, and roentgenograms exposed no defects in the nasal or orbital bones or in the cribriform plate. The mass was removed by operation, during which it was discovered to extend through the wall of the nose down to the mucous membrane. The tumor and a small piece of nasal mucosa were excised. The patient's recovery was uneventful.

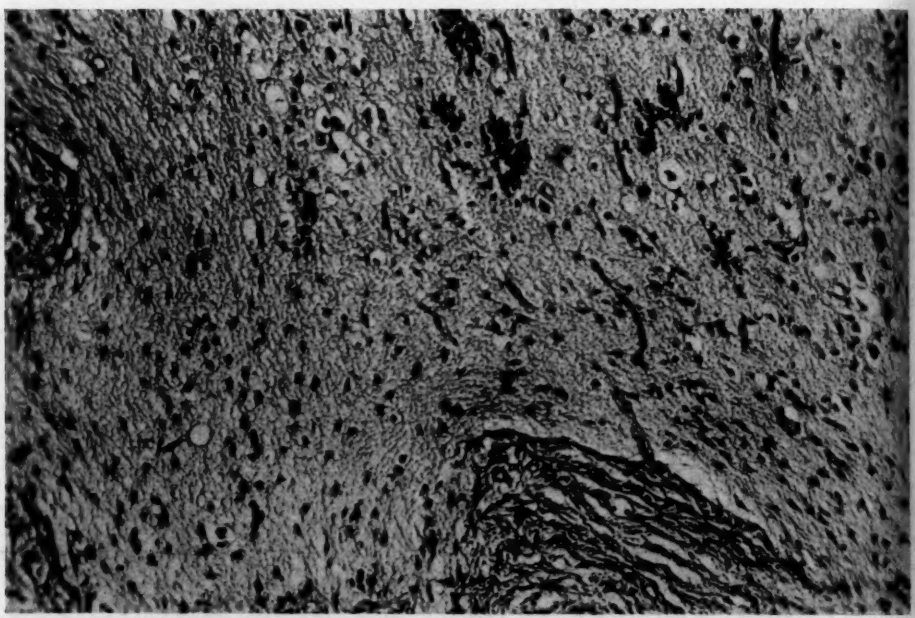

Fig. 3 (case 2).—Large sheet of glial tissue within the corium from a section of the tumor removed at the original operation. Hematoxylin-eosin stain; × 230.

Sections of the original tumor of this case (fig. 3) have been described and reported by Dr. J. W. Hill.[10] As he observed, there were several large masses of delicate fibrillary glial tissue in the corium, beneath essentially normal skin. Moderate numbers of capillaries and small vessels with thick endothelium were present throughout. The cells of the glia all resembled astrocytes, although a few were enlarged and there were some multinucleated forms. These cells were specifically impregnated by Cajal's gold chloride–mercury bichloride method for astrocytes, as illustrated in Dr. Hill's report. The fibrils also stained blue with Mallory's phosphotungstic acid–hematoxylin. The fibrous tissue about the glial masses was in narrow strands and not remarkable. A few small calcified spheroid bodies

10. Hill, J. H.: Glioma of the Nose: Report of a Case of the Extranasal Type, Arch. Path. **48**:183 (Aug.) 1949.

were present throughout the tumor. This tumor differed from that of case 1 principally in the larger masses of glial tissue and the less prominent part of the tumor comprised of fibrous septums.

The recurrent tumor (fig. 4) was composed of a large amount of glial tissue, which was separated into strands by fibrous septums. The glial tissue contained only cells with the appearance of astrocytes, although there were many multinucleated and distorted forms. No mitotic figures were present. With the Mallory phosphotungstic acid–hematoxylin stain the fibrils of the strands were a typical blue. No neurofibrils were indicated by the Gros-Bielschowsky method. The fibrous septums were much more prominent than in the original tumor of

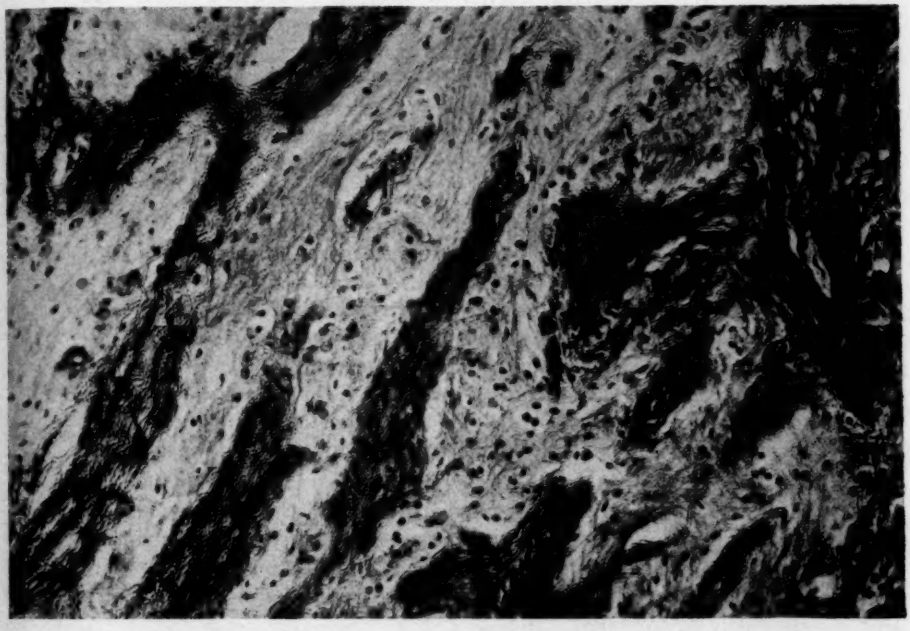

Fig. 4 (case 2).—Strands of glial tissue between very dense bands of collagen in the recurrent tumor. Phosphotungstic acid–hematoxylin stain; × 230.

this case but formed a smaller proportion of the tumor than did the similar structures in the original tumor of case 1. They also did not have the somewhat organized appearance about central blood vessels present in the first case. No foci of calcification were present in the recurrent tumor.

ANALYSIS OF REPORTED CASES

The tumors in the two cases presented are unusual in that they grew at a faster rate than the surrounding tissue. Although in their histological features these tumors were not distinguishable from those of other reported tumors of this type, the history of their course indicates

that they were composed of tissue with potentiality for more nearly autonomous growth than might be expected of a simple heterotopia or malformation. The occurrence of these tumors in the extranasal site afforded the most favorable conditions for accurate determination of the gross characteristics, extent and connections of the tumors by exposure at operation. The case reported by Eigler [11] (case 21) is the only other in the literature which afforded opportunity to observe the isolated nature of the tumor in an extranasal position and the growth of a recurrence. In that case the tumor developed as a definite mass during a period of several years, although some defect, described as a "fleck," had been present since the patient was at least 6 years of age. The tumor recurred within three months after excision, and the recurrent tumor contained glial tissue. In the case reported by Seiferth [12] (case 13) a tumor developed during a period of four years on the bridge of the nose of an adult. Although there was no recurrence, that case also contributes evidence of accentuated growth potential in occasional tumors of this type.

More commonly the extranasal glioma is a congenital mass that is discovered soon after birth and removed without complications or recurrence. Ten cases of such tumors have been reported and are summarized in the accompanying table as cases 1, 4, 7, 26, 27, 30, 31, 32, 33 and 34. New and Devine [13] had previously reported certain features of three of the cases and have now supplied us by personal communication with additional data, summarized in the table, concerning those cases and a fourth case they have recently observed.[14] They have also allowed us to review the microscopic preparations of the tumors in their cases; these sections are essentially similar to those of other tumors of this type.

The histories of the majority of cases of extranasal glioma indicate that the tumors were masses of glial tissue which had grown during intrauterine development at a rate not necessarily faster than the normal glia within the central nervous system. The mature histological appearance and lack of evidence of autonomous growth suggest that they were essentially heterotopias.

A significant group is that of eight cases (5, 11, 12, 14, 15, 19, 22 and 25) of solid, extranasal glial tumors not covered by meninges but associated with an underlying defect of the bone and attached by a

11. Eigler, G.: Drei seltene Geschwülste der oberen Luftwege: (Fibrorhabdomyoma laryngis; Neurofibroma laryngis, Glioblastoma nasi), Hals-, Nasen- u. Ohrenarzt. **28** (pt. 1): 320, 1937.

12. Seiferth, L. B.: Beiträge zur Lehre von den Geschwülsten der Nasennebenhöhlen unter besonderer Berücksichtigung der Multiplizität und Aetiologie der Tumoren, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres. **25**: 177, 1927.

13. New, G. B., and Devine, K. D.: Neurogenic Tumors of the Nose and Throat, Arch. Otolaryng. **46**: 163 (Aug.) 1947.

14. New, G. B., and Devine, K. D.: Personal communication to the authors.

Case No.	Author	Date	Age of Occurrence (Yr.)	Sex	Location	Growth	Comment
1	Schmidt	1900	Congenital	M	Extranasal; right side	None	No recurrence in 3 yr.
2	Clark	1905	Congenital	M	Extranasal, intranasal; midline	None	.....
3	Clark	1905	Congenital	M	Intranasal; left side	None	.....
4	Süssenguth	1909	Congenital	M	Extranasal;	None	.....
5	Comninos	1911	Congenital	F	Extranasal; midline	Slight enlargement	No glia in stalk; bony defect present
6	Anglade and Philips	1920	Congenital	M	Intranasal; right side	Recurrence in 3 mo. and again in 2 wk.	No microscopic description of recurrent tumors
7	Berblinger	1920	Congenital	?	Extranasal; left side	None	.....
8	Terplan and Rudofsky	1926	13 yr.	F	Intranasal; left side	Obstruction of nose in 7 wk.	.....
9	Guthrie and Dott	1927	46 yr.	M	Intranasal; left side	None	Operation for nasal polyps 4 and 5 yr. before; tumor attached to middle turbinate bone; no recurrence in 7 yr.
10	Rocher and Anglade Case 2	1927	Congenital	?	Extranasal, intranasal; right side	None	Tumor contained ependymal cells
11	Case 3	1927	Congenital	M	Extranasal; right side	None	Rare ganglion cells
12	Case 4	1927	Congenital	?	Extranasal; right side	Slight enlargement in 18 mo.	Attachment pedicle unknown
13	Seiferth	1927	33 yr.	M	Extranasal; right side	Development over 4 yr.	Nasal polyps removed 10 yr. before
14	Browder	1929	Congenital	F	Extranasal; midline	None	Pedicle attached to each anterior lobe of brain
15	Cordes	1929	Congenital	F	Extranasal; right side	None	Cyst enlarged with crying; encephalitis followed operation
16	Tobeck	1929	40 yr.	M	Intranasal; right side	? Growth during 5 yr.	Tumor in maxillary sinus; arose from middle turbinate body
17	Adler	1930	19 yr.	F	Intranasal; left side	Obstruction in 3 mo.	Tumor in maxillary sinus; arose from middle turbinate body; extensive degeneration and calcification
18	Adler	1931	24 yr.	F	Intranasal; right side	Progressive obstruction	Arose from lateral wall of nasal cavity; extensive degeneration and calcification
19	Févre and Huguenin	1936	Congenital	?	Extranasal; left side	None	Rare ganglion cells; attachment stalk unknown
20	Zöllner	1936	Congenital	F	Intranasal; left side	Recurrence in 1 mo.	No microscopic description of recurrence
21	Eigler	1937	10 yr.	M	Extranasal; right side	Recurrence in 3 mo.	.....
22	Mood	1938	Congenital	F	Extranasal; right side	None	Capsule of tumor attached to dura
23	Crook	1940	Congenital	M	Intranasal; right side	None	Contained ganglion cells; stalk attached to left maxillolacrimal suture
24	Schwartz and Isaacs	1941	Congenital	M	Intranasal; right side	Slow enlargement	.....
25	Davis	1946	Congenital	F	Extranasal; left side	Slight enlargement	Few probable nerve fibrils
26	Bratton and Robinson	1946	Congenital	F	Extranasal	None	.....
27	New and Devine Case 1	1947	Congenital	M	Extranasal; right side	None	Residual deformity of nose
28	Case 2	1947	Congenital	F	Extranasal, intranasal; right side	?	.....
29	Case 3	1947	Congenital	M	Extranasal, intranasal; right side	None	.....
30	Eggston and Wolff *	1947	Congenital	F	Extranasal	None	Few nerve cells
31	Zettergren	1948	Congenital	M	Extranasal; left side	None	Ganglion cells present
32	Hill (Black and Smith 2)	1949	Congenital	M	Extranasal; left side	Recurrence removed 14 mo. after first operation	Recurrent tumor composed of glia
33	New and Devine: Personal communication	1949	Congenital	M	Extranasal; right side	None	.....
34	Black and Smith Case 1	1950	Congenital	M	Extranasal; left side	Recurrence removed 35 mo. after first operation	Recurrent tumor composed of glia

* Eggston, A. A., and Wolff, D.: Histopathology of the Ear, Nose and Throat, Baltimore, Williams & Wilkins Company, 1947, p. 774.

stalk of fibrous or glial tissue to the contents of the cranium. In the case reported by Davis [15] (case 25) serial sections were made of the region of the nose underlying the tumor. It was demonstrated that a small defect filled with connective tissue was present in the left nasal bone but that the glial tissue of the tumor was an isolated mass. Mood [16] (case 22) reported a case in which an isolated glial tumor was surrounded by a fibrous capsule continuous with the dura In the reports of the third and fourth cases of Rocher and Anglade [2] (cases 11 and 12) the site of origin and the nature of the stalk of the tumor are not stated. Browder [17] (case 14) reported a tumor with a pedicle of grossly fibrous appearance which extended into the cranial cavity, where it divided and was attached to each frontal lobe; and Févre and Huguenin [18] (case 19) stated that the tumor in their case had a pedicle, but they did not specifically locate the site of attachment. Similarly, the tumor reported by Cordes [19] (case 15) had a stalk attached to an undetermined site in the brain. This tumor was reported to enlarge when the patient cried, and there was a postoperative complication of "encephalitis," which was not fatal. These cases represent a transitional group between the tumors completely isolated from the central nervous system and those of encephalocele type.

As noted in the description of the second case reported here (case 32), in some instances a single tumor is present both extranasally and intranasally. The first case reported by Clark [20] (case 2), the second case of Rocher and Anglade (case 10) and the second and third cases of New and Devine (cases 28 and 29) were also of this nature. These cases indicate a close relation between the extranasal and the intranasal tumors composed of glial tissue.

It is considerably more difficult to determine the exact attachments or extensions of the tumors which occur within the nose, as neither operative nor roentgenographic technics permit as complete an examination as is possible with the extranasal tumors. It is often questionable whether the intranasal tumor can be safely distinguished from true encephalocele; but, particularly in the older literature, the incidence of

15. Davis, E. W.: Gliomatous Tumors in the Nasal Region, J. Neuropath. & Exper. Neurol. **1**:312, 1942.

16. Mood, G. F.: Congenital Anterior Herniations of the Brain, Ann. Otol., Rhin. & Laryng. **47**:391, 1938.

17. Browder, J.: Encephaloma or So-Called Nasal Glioma, Ann. Otol., Rhin. & Laryng. **38**:395, 1929.

18. Févre, M., and Huguenin, R.: Encéphalocèle atypique réalisant une tumeur solide à la racine du nez, Ann. d'anat. path. **13**:333, 1936.

19. Cordes, E.: Die Hirnbrüche und Hirnspalten, Ergebn. d. Chir. u. Orthop. **22**:258, 1929.

20. Clark, J. P.: Glioma of the Nose: Report of 2 Congenital Cases, Am. J. M. Sc. **129**:769, 1905.

fatal meningitis following operative intervention in cases of intranasal encephalocele [21] is almost universal. An uncomplicated postoperative course combined with other compatible features is therefore fairly acceptable evidence of the isolation of the glial tissue from the central nervous system. Five cases of intranasal glioma present at the time of birth have been reported and are summarized as cases 3, 6, 20, 23 and 24 in the table.

Among the reports of intranasal tumors are two in which it is suggested that the tumor possessed a capacity for limited growth. Anglade and Philip [22] (case 6) reported a case in which a congenital intranasal tumor recurred within three months after removal to such a degree that a second operation was performed. Fifteen days later a second, small, recurrent mass was observed, and roentgen therapy was applied, which halted its enlargement. No histological examination of either of the recurrent masses was recorded. In the case reported by Zöllner [23] (case 20), a tumor was partially removed from the left nasal cavity after birth, and more complete removal was attempted when the patient was 14 months of age. One month later a small mass, referred to as a recurrent tumor, was seen, and this mass was present at the last reported observation, when the patient was 4 years old. No biopsy of the recurrent mass was recorded. The absence of histological proof that the recurrent masses in these cases were actually composed of glial tissue, as described in the original tumors, is disappointing.

In addition to the cases of congenital intranasal glioma, five cases have been reported in which the attention of the patient was first attracted during or after childhood to an intranasal tumor (cases 8, 9, 16, 17 and 18). In the first case reported by Terplan and Rudofsky [24] (case 8), that of a girl 13 years of age, the tumor had the focally palisaded appearance of some astrocytomas (polar spongioblastomas) that arise in the central nervous system. In the case reported by Guthrie and Dott [25] (case 9) the glial element of the tumor was an incidental histological observation following removal of what were interpreted as recurrent nasal polyps. The observations in neither of these cases establish the growth of the tumor itself, and it may be suggested that

21. Natanson, L.: Über intranasale Cephalocelen, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **135**:103, 1933.

22. Anglade and Philip: Le gliome des fosses nasales, Presse méd. **28**:464, 1920.

23. Zöllner, F.: Angeborenes Gliom der Nase? Frankfurt. Ztschr. f. Path. **49**:82, 1935.

24. Terplan, K., and Rudofsky, F.: Über zwei neurogene Tumoren in der Nasen- und Mundhöhle, Ztschr. f. Hals-, Nasen- u. Ohrenh. **14**:260, 1926.

25. Guthrie, D., and Dott, N.: The Occurrence of Brain Tissue Within the Nose: The So-Called Nasal Glioma, J. Laryng. & Otol. **42**:733, 1927.

the glial tissue was congenitally present and that symptoms arose as a result of secondary increase in volume, such as may follow chronic inflammation. The other three intranasal tumors which were not congenital were unusual. In the case reported by Tobeck [26] (case 16) the tumor had extended into the maxillary and ethmoid sinuses. In one of the cases reported by Adler [27] (case 17) the tumor also extended into the maxillary sinus. However, the tumors in both cases described by Adler [27] (cases 17 and 18) contained extensive focal calcification and degeneration, which made recognition of their glial origin difficult and questionable. The presence of a few blue fibrils in sections of one of these tumors stained by Mallory's phosphotungstic acid–hematoxylin method was the most objective feature suggestive of glial tissue described by that author.

In final commentary of the compilation of the cases listed in the table, certain omissions should be explained. A case was excluded when the tumor described was composed of glial tissue in obvious continuity with that of the central nervous system and had features characteristic of a true encephalocele, such as a central cavity in communication with the cerebral ventricles or a subcapsular space filled with cerebrospinal fluid. On this basis, the first case of Rocher and Anglade [2] was excluded, as these authors stated that cerebrospinal fluid was aspirated from the extranasal mass and continued to drain from the ensuing fistula until the patient died of meningitis. Reference is often made to a case reported by von Meyer [28] because it established that an intranasal mass could be composed of glial cells without ganglion cells; but that author was in no doubt that the tumor was an encephalocele, and he clearly described the defect in the bone, the connection with the brain and the coverings of dura, arachnoid and pia. The case of Dellepiane Rawson and Vivoli [29] is also interpreted as an encephalocele for similar reasons, as stated by Davis.[15] Rocher and Lange [30] presented a case before the Anatomico-clinical Society of Bordeaux in 1933, but the brief report published does not provide sufficient data to permit its accurate classification, although Rocher had previously described tumors of this type and was undoubtedly

26. Tobeck, A.: Über das Vorkommen und die Entstehung neurogener Geschwülste im Bereiche der Nase, Ztschr. f. Hals-, Nasen- u. Ohrenh. **23**:329, 1929.

27. Adler, H.: Ein Beitrag zu neurogenen Geschwülsten der Nase, Ztschr. f. Hals-, Nasen- u. Ohrenh. **26**:305, 1930.

28. von Meyer, E.: Über eine basale Hirnhernie in der Gegend der Lamina cribrosa, Virchows Arch. f. path. Anat. **120**:309, 1890.

29. Dellepiane Rawson, J., and Vivoli, D.: Les fibrogliomas de la región nasal, Rev. méd. latino-am. **14**:860, 1929.

30. Rocher, H. L., and Lange, J.: Sur un cas de fibrogliome de la région naso-frontale gauche, Gaz. hebd. d. sc. méd. de Bordeaux **54**:287, 1933.

aware of their nature. Berger and Richard [31] and Berger and Coutard [32] described tumors which have occasionally been referred to as varieties of nasal glioma, but these authors carefully distinguished them from the "fibrogliomas" of Anglade and Philip. These tumors were probably neuroepitheliomas or neurocytomas, tumors which differ so distinctly from nasal gliomas that they are not germane to this discussion. The first case of Bratton and Robinson [33] was excluded because the tumor occurred on the palate and, although called a glioma, contained such a mixture of elements that the authors suggested, apparently very properly, that it was basically a teratoma. Finally, Guthrie and Dott [25] reported as their first case that of a cerebral glioma which had extended into the nose via a defect in the cribriform plate and properly distinguished it from the tumors more commonly referred to as nasal gliomas.

Two obscure references were found, one by Portmann and Beillard [34] to a case reported by Passow in 1898, and the other by Berger and Richard [31] to a case reported by Fisher in 1918, which could not be confirmed by intensive search of the medical indexes of the respective periods or the original journals to which reference was made.

CLINICAL CHARACTERISTICS

From this survey the following clinical features are noted. The extranasal tumors are usually on the right or the left side of the bridge of the nose. Of these collected cases, 12 occurred on the right side, seven on the left side and two in the midline. The diameters of the tumors varied from 1 to 3 cm. The sex of the patient was stated in 19 cases; 12 patients were males and seven were females. The root of the nose is often described as broadened and the eyes as more widely separated than normal. The tumors are firm and elastic and occur subcutaneously. Occasionally the overlying skin is discolored. There are neither pulsations nor changes in size when the patient cries or strains. Detectable defects in the underlying bone are an inconstant feature.

In five of the present series a single tumor was present both intranasally and extranasally. The sex of 10 patients with intranasal glioma was indicated; six were males and four females. Five tumors occurred on the right side and five on the left side of the nose. The intranasal

31. Berger, L., Luc and Richard: L'esthésioneuroépithéliome olfactif, Bull. Assoc. franç. p. l'étude du cancer **13**:410, 1924.

32. Berger, L., and Coutard, H.: L'esthésioneurocytome olfactif, Bull. Assoc. franç. p. l'étude du cancer **15**:404, 1926.

33. Bratton, A. B., and Robinson, S. H. G.: Gliomata of the Nose and Oral Cavity: Report of 2 Cases, J. Path. & Bact. **58**:643, 1946.

34. Portmann, G., and Beillard, P. F.: Les tumeurs nerveuses de fosses nasales, Rev. de laryng. **08**:125, 1947.

tumors are occasionally confused with nasal polyps, from which they may be distinguished only by their firmer consistency. An accurate estimation of the size of intranasal tumors is not possible because of their position. They arise high in the nasal fossa. The septum and nasal bones are often displaced, and the nasal passageway is blocked on the side of the tumor. In the present series, every intranasal glioma which was not congenital arose from the middle turbinate bone or the lateral wall of the nasal fossa, in contrast to the intranasal encephalocele, which Hallermann [35] stated is usually attached to the nasal septum. Many other tumors and some encephaloceles have characteristics similar to those of the intranasal glioma, and there is no way of establishing the diagnosis before biopsy or removal of the mass.

ANATOMIC CHARACTERISTICS

The gross appearance of the tissue of the nasal glioma after removal has been described in very few reports. The most frequently mentioned feature is its firm consistency, and it rarely is recognizable grossly as brainlike tissue. This lack of resemblance is probably due to the variable histological composition, which ranges from predominantly glial to predominantly fibrous tissue. The fibrous tissue is usually prominent in sections and lies as septums separating the masses of glia. The vascularity and membranous organization that are sometimes features of these septums are the characteristics which led Schmidt to compare them to the leptomeninges. The glial tissue is composed largely of astrocytes and their processes and is generally very similar to that of the stroma of the central nervous system. In many cases enlarged, irregular forms have been described among the astrocytes, and some may be multinuclear. Mitotic figures are rare or absent. Only a few tumors, notably one described by Terplan and Rudofsky [24] (case 8), have had sufficient cellular irregularity to resemble a true glioma of the central nervous system. Small nests of ependymal cells and canals lined with ependyma were described in one tumor by Rocher and Anglade (case 10).

True neuronal cells are rare, although they were conclusively demonstrated by means of special stains by Zettergren [3] (case 31) in the tumor he reported. Four other authors have mentioned their presence in particular tumors, and a few neurofibrils were described in another tumor, although no cells were recognized. Several authors have commented on the resemblance of the giant glial cells to ganglion cells, and their differentiation is occasionally difficult. In most instances the appearance of the ganglion cells suggests that they are degenerate forms,

35. Hallermann, O.: Intranasale Meningocelen und ihre klinische Diagnose, Ztschr. f. Hals-, Nasen- u. Ohrenh. **30**:413, 1932.

although in Crook's case [36] (case 23) James Ewing [37] made the diagnosis of "a true neoplasm" on the basis of "great irregularity in the distribution of nerve tissue and pronounced increase in the number of ganglion cells which are often quite atypical."

PATHOGENESIS

Since Schmidt's [6] original description of a nasal glioma, most authors have accepted in principle his theory of origin. He postulated that the tumor was originally an encephalocele that had been cut off from the brain during embryonic development by closure of embryonic sutures of the skull. He explained the intimate relation of the connective tissue, in the tumor he reported, by postulating that it represented the meninges and their prolongations into the brain. This theory has been reenforced by the reported similar appearance of certain encephaloceles and nasal gliomas. Berger [4] stated that some encephaloceles may be composed entirely of glial tissue, that the irregular cells indicate they are true new growths and that they should be called encephalomas. Zöllner,[23] basing his conclusions in part on the work of von Meyer,[28] agreed that encephaloceles may be completely unorganized and contain no neural elements, and thus closely resemble nasal gliomas. Browder and deVeer [38] have emphasized this microscopic similarity. They speculated that there is a close etiological relation between these tumors and rhinencephaloceles and that nasal gliomas might be derived from the rhinencephalon. Rocher and Anglade [2] suggested that they may arise from the olfactory lobe, as well as the anterior vesicle in early embryonic development. Guthrie and Dott [25] and Clark [20] deviated from Schmidt's theory only in that they suggested that the portion of brain tissue was pinched off early in embryonic development, before there was differentiation of glial tissue.

Süssenguth [39] stated that the theory of origin from an encephalocele was inadequate to explain the extranasal lesions, and he postulated that these growths were heterotopias of olfactory origin. He stated that in early embryonic development a relatively large projection arises from the frontal process of the cerebral vesicle to form the olfactory bulb. As the brain develops, the olfactory process shrinks to form the olfactory nerve. At any time in this regression a portion may become separated

36. Crook, M.: Congenital Ganglio-Neuroma of the Nose: Report of Case, J. South Carolina M. A. **36**:159, 1940.

37. Ewing, J., cited by Crook [36] as personal communication.

38. Browder, J., and deVeer, J. A.: Rhino-Encephalocele, Arch. Path. **18**:646 (Nov.) 1934.

39. Süssenguth, L.: Über Nasengliome, Virchows Arch. f. path. Anat. **195**:537, 1909.

and later isolated by closure of the frontal bones. Berblinger,[40] basing his argument on the contention that the encephalocele could not be expected to regress into an isolated solid tumor, stated the opinion that this lesion was in most instances a true heterotopia of olfactory origin.

Several features of the embryonic development in the region of the nose are helpful in elucidating the location and development of the nasal glioma. Schmidt [6] and Zettergren,[8] among others, called attention to the work of Holl,[41] who demonstrated that the fibrous process of dura which normally seals off the foramen cecum is the remnant of an earlier cord of epithelial cells that extends to the tip of the nose of the embryo. Failure of proper development of this process might leave a pathway along which glial tissue could extend to the sites at which nasal gliomas and encephaloceles occur. Sternberg,[42] writing particularly of nasal encephaloceles, made reference to the anterior neuropore, which opens in the primordial nasal region of the embryo and as late as the 28 segment stage is normally present as a solid cord of cells of epithelial origin. Persistence of such cells along the former course of this cord might furnish cells capable of maturing into glia. Whether nasal gliomas arise from such persistent cells which later mature into glia or are extruded from the embryonic brain is somewhat incidental, for even such a phenomenon must occur early in gestation, before the nasofrontal articulations normally close, if an isolated tumor is to result.

Tobeck [26] deviated considerably from the theory of pathogenesis from encephaloceles and advanced a theory based on the embryology of the olfactory placode. The placode is an ectodermal structure which arises independently from the brain. It contains cells which are homologs of glial cells and others which are homologs of ganglion cells. The placode grows centrally to come into contact with the brain during embryonic development. Tobeck postulated that either gliomas or neurocytomas might arise in this manner. Anglade and Philip [22] suggested that certain of the nasal gliomas might develop from neuroglial cells in the nasal mucosa, which had been demonstrated along the axons of the olfactory cells by Ramón y Cajal.[43] The theories of origin from the olfactory placode and of glial cells in the nasal mucosa entirely fail to account for the extranasal tumors. They, together with the theory of the unilateral development of a teratoma, have never been generally accepted.

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40. Berblinger, W.: Gliom von seltener Lokalization, Centralbl. f. allg. Path. u. path. Anat. **31**:201, 1920.

41. Holl, cited by Schmidt.[6]

42. Sternberg, H.: Zur formalen Genese der vorderen Hirnbrüche (Encephalomeningocele anterior), Wien. med. Wchnschr. **79**:462, 1929.

43. Ramón y Cajal, S., cited by Anglade and Philip.[22]

COMMENT

A study of glial tumors in the region of the nose reveals a continuous series of lesions, varying from a characteristic encephalocele, with an ependyma-lined space communicating with the ventricles and filled with cerebrospinal fluid, to a solid mass of glial tissue which is entirely separate from the brain and has limited potentialities of autonomous growth. The transitional stages include lesions with a microscopic canal lined with ependyma within solid tissue which may or may not be connected with the brain; lesions without ependymal cells but with an indefinitely attached pedicle, and solid lesions without a pedicle but attached to the dura with a band of fibrous tissue. It is difficult to determine which of these lesions should be designated as nasal gliomas and yet retain differential significance for the term. From a practical standpoint, this series can be divided into encephaloceles, which contain a fluid-filled extension of the subarachnoid and ventricular spaces, and solid tumors, which do not contain such spaces. The risk of incurring cerebral complications after surgical removal is obviously greater for lesions of the first group than for those of the second. The presence or absence of a pedicle connected with the brain cannot be used as a practical criterion in defining a nasal glioma, since in the case of intranasal tumors, particularly, it may be difficult or impossible to determine its extent or course. The presence or absence of small canals lined with ependymal cells cannot be considered significant because these cells may be included incidentally in the process of formation of the tumor.

The presence or absence of ganglion cells is apparently fortuitous and is probably a reflection of the embryonic stage of development at which the encephalocele occurred. The ganglion cells appear at the periphery of the brain at a later date than do the glial cells. The absence of ganglion cells in some instances may be due to the susceptibility of these cells to relative anoxia. The bizarre astrocytes that may be prominent in these lesions have been interpreted as evidence of malignancy (Eigler,[11] Ewing [87] and Schwartz and Isaacs [1]), but these changes could be those of gliosis, rather than neoplasia, and due to circulatory impairment.

The ability of a particular nasal glioma to grow cannot be predicted, since the microscopic picture of those that have recurred is identical with others that have not. In most instances the growth potential is rather low, and adequate removal will be followed by complete cure. The occasional occurrence of nasal gliomas in adults may be explained as due to delayed growth or to delayed recognition of the presence of the tumor. Some nasal gliomas reported as occurring in adults were intranasal, and thus not subjected to close observation; but in the cases of Eigler (case 21) and Seiferth (case 13) there was without doubt relatively sud-

den increase in size. Even though this difference in growth ability is apparent, it is not considered sufficiently significant to warrant creation of a separate category for those tumors in which it is evident.

Some of the various names that have been applied to this tumor have certain points in their favor. Choristoma,[33] for instance, might well be applied to those tumors which give definite evidence of growth either before or after surgical intervention, since they are new growths developing from a misplaced anlage. This term would serve to differentiate them from the glial masses which are separate from the brain and show no apparent increase in size or tendency to recur. The latter could be designated as heterotopias, since they consist of mature tissue in an abnormal location. To those tumors that show a definite attachment to the brain but have no ventricular or meningeal continuity the term encephaloma[17] could be used. Such a variety of names serves only to confuse the issue, since the various cases represent a continuous series from choristoma to encephalocele. While the term nasal glioma is certainly open to criticism because most of these lesions do not show autonomous growth, this term is so intrenched in the literature that it might well be retained.

Therefore, the term nasal glioma should be used to designate a mass of glial tissue of congenital origin which occurs intranasally and/or extranasally at or near the root of the nose, which may or may not be connected to the brain by a pedicle of glial tissue and which in some instances has an ability to grow autonomously.

The original theory of pathogenesis, as advanced by Schmidt, seems to be essentially correct. The series of cases presenting a gradual transition from encephalocele to a discrete mass of glial tissue certainly points to such an origin of these tumors. The location of nasal gliomas in locations similar to those of the basal and sincipital encephaloceles is further evidence of an etiological relation. The occurrence of similar solid masses of glial tissue in the area of occipital encephaloceles indicates that the same principle of formation may function elsewhere.

SUMMARY

A nasal glioma is a mass of glial tissue of congenital origin that occurs intranasally and/or extranasally at or near the root of the nose. It may or may not be connected to the brain by a pedicle of glial tissue, but it does not contain a fluid-filled space connected with either the ventricles or the subarachnoid spaces of the brain.

Two cases are reported in which there was recurrent growth of such a tumor after grossly complete surgical removal. This indicates that some of these lesions have characteristics of low grade neoplasia.

A tabulation of previously reported cases is made, and attention is drawn to the etiological significance of the transitional forms from encephaloceles to nasal gliomas within the series.

PREVALENCE AND INCIDENCE OF MULTIPLE SCLEROSIS IN BOSTON, 1939-1948

Preliminary Report

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THE BROAD epidemiological characteristics of multiple sclerosis in Boston and Brookline, Mass., for the years 1939 to 1948, inclusive, have been studied as a part of a national survey by six independent groups of investigators, having as its purpose the determination of the frequency of the disease in representative regions of the United States and Canada. Knowledge of incidence and prevalence of cases and of frequency of deaths is a basic requirement in appraising the total costs of a disease to a community. For a chronic disease annual rates of incidence and prevalence tend to differ widely, in contrast to those for most acute diseases, for which the two values are much the same. Incidence is a measure of the rate at which new cases appear in a population during the prescribed year, while prevalence is the frequency of all cases existing during that time, including new cases and those carried over from preceding years.

The collection of epidemiological data on multiple sclerosis is complicated by the inherent and unusual characteristics of the disease. Ten years of observation were deemed necessary to obtain informative rates. The insidious onset and the frequent remissions often lead to a delay of several years in the first visit to a physician, until symptoms are pronounced. Both factors contribute to delayed diagnosis, with the result that the actual onset of the disease often dates back a number of years. Multiple sclerosis is, of course, not a reportable condition. Frequency data based on hospital admissions are incomplete, since many patients are treated at home. Despite the common high grade disability, the usual reason for admission to the hospital is confirmation of the diagnosis or treatment of complications. On the other hand, many patients visit a number of hospitals or physicians in a given period, a

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These studies were aided by a grant from the National Multiple Sclerosis Society.

situation requiring that individual cases be identified if they are not to be duplicated in tabulations.

Mortality data, the principal reliance of the epidemiologist in many diseases, are of limited value in multiple sclerosis. The disease is not an important cause of death in a general population, although it is responsible for much disability. Death certificates commonly fail to include the diagnosis of multiple sclerosis when an intercurrent disease is the immediate cause of death. Errors frequently arise in official vital statistics through listing as multiple sclerosis other diseases, such as cerebral arteriosclerosis.

COLLECTION OF DATA

The number of patients with multiple sclerosis resident in Boston and Brookline between Jan. 1, 1939 and Dec. 31, 1948 was determined by field survey. Brookline was included because Boston almost completely surrounds that town, and the two are essentially a single community at the center of the metropolitan area. House to house survey was judged a poor method for this study because of the relative rarity of the disease and because difficulties in diagnosis require thorough clinical study. Three main sources of data were available: a scrutiny of hospital records for the period, interviews with practicing physicians and examination of death certificates. The survey, made between June 1 and Oct. 15, 1949 used these three sources of information.

Through cooperation of staffs of record rooms, selected senior medical students extracted case records of hospital patients admitted between 1939 and 1948. All hospitals of the Boston-Brookline area were included, and, in addition, neighboring hospitals under the Veterans Administration, the Tewksbury State Hospital and Infirmary for chronic diseases and several nursing homes. The patient's name was recorded in the Russell-Soundex code to secure both anonymity and a system whereby duplicate records could be identified.

A circular letter was sent to the 2,605 physicians of Boston and Brookline asking whether or not they had treated patients with multiple sclerosis during the given period. Prompt answers from a high proportion of physicians was evidence of unusual collaboration and interest. Visits were made to physicians who had seen patients, and pertinent data were collected for each case. Physicians not replying to the first survey letter were visited personally or interviewed by telephone, with the result that information was obtained from 87 per cent of the 1,818 practicing physicians, a satisfactory proportion in any circumstances, and especially for a survey conducted during the summer months. Of 787 full time hospital staff members, 417 gave answers. Further contact was not sought, since presumably most patients known to them were covered by the hospital survey.

Death certificates of persons who died of multiple sclerosis in Boston and Brookline from 1939 to 1948 were identified through serial numbers obtained by sorting the 500,000 punched cards in files of the Department of Health of the Commonwealth of Massachusetts. There were 74. Using these serial numbers, the actual death certificates were located in the ledgers of the city health department. Certificates from 1948, not yet on punch cards, were directly available through courtesy of the city health department.

These three studies, in record rooms of hospitals, by interview of physicians and through study of death certificates, gave 1,115 reports of patients with multiple sclerosis. Some were represented several times, in one instance nine times, so that the 1,115 reports resolved into 797 firmly established cases.

Fourteen cases, identified from death certificates alone, were excluded because of obvious errors in classification, such as cerebral tuberous sclerosis in a 9 year old boy and, in several instances, cerebral arteriosclerosis of elderly patients. Thus, 783 cases remained for analysis. That all were actual cases of multiple sclerosis cannot be established. Survey investigators recorded all patients with that diagnosis when the clinical evidence was at least suggestive. Since no absolute diagnostic criteria for multiple sclerosis exist, the material contained a number of borderline cases. The probability of correct diagnosis depends on a variety of information, such as multiplicity of lesions, typical remissions and confirmation by several hospital admissions or consultations by specialists. All patients in the present series were assigned the diagnosis of multiple sclerosis by a competent physician at least once.

After careful study of available facts, the material was arbitrarily divided into two groups of cases, the more doubtful being classified as possible cases of multiple sclerosis, while those with records presenting convincing evidence were classed as probable cases. The intent was to permit reasonable definition of

TABLE 1.—*Distribution of Cases of Multiple Sclerosis in Boston and Brookline by Source of Record, Sex and Reliability of Diagnosis (1939-1948)*

	Diagnosis						
	Probable (602)		Possible (181)		Total		
Source of Record	Male	Female	Male	Female	Male	Female	All Cases
Hospital	127	231	54	73	181	304	485
Physicians only	67	145	23	31	90	176	266
Death certificates only	11	21	..	..	11	21	32
Totals	205	397	77	104	282	501	783

limits for incidence, mortality and prevalence. For a few of the 783 cases the diagnosis of multiple sclerosis was suggestively outside the limits of probability. On the other hand, to restrict cases to those in which the diagnosis was beyond doubt would reduce the number to those proved by autopsy. The general level of medical competency in the Boston area warrants assumption that most diagnoses are acceptable. It is not to be inferred that all listed as "possible" cases were not true cases; nor the opposite, that the probable cases were undoubted, for both groups are subject to errors in interpretation. The number of actual cases would appear to be somewhere between the number of probable cases and the total number brought out by the survey (table 1).

The 783 cases of the survey were divided according to sources of information by which they were identified, by presumed reliability of diagnosis and by the sex of the patient. Cases included in the category "hospital" were from records of hospitals and outpatient clinics. The category "physicians only" indicates that the patient had no record of admission to a hospital. In the third category of table 1 are cases in which the information was from death certificates only.

Some 62 per cent of patients had been admitted to hospitals during the 10 year period; 34 per cent had been under the care of private physicians, and only 4 per cent came to knowledge through death certificates alone. In a study in Sweden, 1925 to 1935, Sällström [1]

1. Sällström, T.: Das Vorkommen und die Verbreitung der multiplen Sklerose in Schweden, Acta med. Scandinav., 1942, supp. 137.

estimated that hospital cases included 95 per cent of all cases occurring in that country. Table 2 shows the Boston experience, that only 37 per cent of patients with onset in the immediately preceding four years (1945 to 1948) were admitted to hospitals. The percentage of hospital admissions for patients with onset earlier than 1945 is somewhat greater. Private practice is evidently an important source of information on early cases.

The two tables also show the limited value of official mortality data in estimating the morbidity of multiple sclerosis. Of 74 recorded deaths in Boston and Brookline, 60 were due to that disease and 14 others clearly to other causes, incorrectly classified as multiple sclerosis. The 60 deaths were only 47 per cent of actual deaths known to have occurred during the study period. On the other hand, only 28 of the 60 deaths were noted in medical records of physicians and hospitals.

TABLE 2.—*Cases of Multiple Sclerosis in Boston and Brookline by Year of Onset and Source of Record (1939-1948)*

Year of Onset	Hospitals	Physicians	Death Certificates	Total	Hospital Cases, Per Cent
1945-1948	49	84	0	133	37
1941-1944	125	82	2	209	60
1937-1940	125	46	9	180	70
1933-1936	63	24	8	95	66
1925-1932	73	14	3	90	81
1917-1924	25	10	3	38	66
1907-1916	6	4	0	10	60
Unknown	19	2	7	28	68
Totals	485	266	32	783	62

Thus, death certificates disclosed only half of the actual deaths of persons with multiple sclerosis. On the other hand, one fourth of the information about fatal cases was derived wholly from this source. The discrepancy between reported and actual deaths is presumably related to the chronicity of the disease. Intercurrent infections or apparently unrelated causes of death (e. g., accidents) can appear as the sole cause of death. Whether multiple sclerosis was actually the principal cause of death could be brought out only by a clinical study of cases. This study views mortality as a public health interest, in which the number of people dying with—and not necessarily from—multiple sclerosis is the particular objective.

ANNUAL PREVALENCE AND INCIDENCE OF MULTIPLE SCLEROSIS

The 873 cases recorded in the Boston area between 1939 and 1948 represent a changing population of patients, some patients having entered during the period of observation and others having withdrawn. With-

drawals were variously because of death, moving out of the area or clinical improvement of such degree that the patient required no further medical attention. For irregular periods these patients were a part of the group. Their subsequent fate is not known; but, from the standpoint of populations of multiple sclerosis in Boston at prescribed periods they were termed "withdrawn" and were excluded from the total number of patients for years following the last observation.

In computing annual prevalence, all cases with onset before 1939 were counted in the first year of observation, 1939, with the ages of patients in 1939 noted. New cases appearing in 1939 were entered in

TABLE 3.—*Multiple Sclerosis in Boston and Brookline with Annual Prevalence, Incidence and Withdrawal of Patients (1939-1948)*

	Probable Cases				Possible Cases					
			Withdrawals				Withdrawals			
Year	Left from Preceding Year	New Cases	Deaths	Unknown* Cause	Left from Preceding Year	New Cases	Deaths	Unknown* Cause	Annual Incidence	Annual Prevalence
1939	285	27	3	16	62	15	0	15	42	389
1940	293	33	13	23	62	20	0	18	53	408
1941	290	39	9	12	64	12	0	9	51	405
1942	308	36	10	17	67	15	2	14	51	426
1943	317	42	10	10	66	10	0	19	52	435
1944	339	41	10	17	57	13	1	12	54	450
1945	353	30	18	21	57	12	0	0	42	452
1946	344	31	17	29	59	7	3	9	38	441
1947	329	24	14	14	54	4	2	9	28	411
1948	325	14	13	26	47	11	2	8	25	397
Annual Means	318.3	31.7	11.7	18.5	59.5	11.9	1.0	12.3	43.6	421.4
Rate per 100,000 †	...	3.9	1.43	..	..	1.45	.12	..	..	51.3

* Last observed in that year.
† Population in 1940: 820,602.

the proper age groups, this constituting the incidence for that year. Together, the numbers give the prevalence for 1939.

To compute the prevalence for 1940, the number of patients who died or were last observed in 1939—together they constitute the number withdrawn—was subtracted from the prevalence for 1939. Next, all cases were moved into the next succeeding annual age group, and the incidence of 1940 was added, to give the prevalence for 1940. Table 3 presents the total prevalence, incidence and withdrawals by years, separated according to reliability of diagnosis.

The annual incidence is of much the same order of magnitude as the withdrawals, with the result that prevalence is maintained at similar levels, with an average of 51 per 100,000, during the 10 years of observation. Only 29 per cent of withdrawals were due to death. Annually, 3 per cent of patients with multiple sclerosis died.

AGE AND SEX DISTRIBUTION

Multiple sclerosis has long been recognized as a disease of adults, but with no clear indication of sex relation. Some observers have found a preponderance of men [2]; others, of women [3] and sometimes no significant difference is determined between the sexes.[1] Much depends on the source of the data and on whether the numbers relate to incidence, to prevalence of cases or to mortality. The situation in respect to age and sex distribution in multiple sclerosis is displayed to best advantage by expressing prevalence, incidence and mortality as age-specific rates.

The general conclusions to be drawn from chart 1 are that in both sexes the disease tends to appear at 10 to 15 years of age (chart 1 *B*) and that the highest incidence is between the ages of 20 and 40 years. For females the average incidence is 1.62 times as great as for males, with differences most pronounced around 20 to 25 years of age, when the incidence for females is about three times that for males.

The sex difference is less evident among deaths (chart 1 *C*). Mortality for females is generally as great (1.34 times) as that for males, but not to the same extent as with incidence. Consequently, prevalence of female patients is distinctly more than that for males (1.74), as is to be expected, since more cases among females occur each year and the mortality for males is not proportionally less.

For both sexes, the age group of highest prevalence is 35 to 40 years, which is about 10 years later than the mode of the incidence distribution, a natural consequence of the chronicity of multiple sclerosis.

DISAPPEARANCE OF CASES

During the 10 year period, 436 new cases of multiple sclerosis appeared in the Boston experience, while 435 cases were withdrawn from the sample. Consequently, the average prevalence of cases was much the same in 1939 and 1948. The question arises whether this balance of income and outgo of cases is a recent phenomenon or whether the situation has prevailed for a number of years. In the absence of data for earlier periods, an inference is sought from the distribution of recorded cases from 1939 to 1948 by year of onset of the disease, as presented in chart 2.

The number of cases decreased rapidly as the interval increased between the time of their onset and 1939, the first year of the observation period. The evident explanation is that a number of patients disappear

2. Kolb, L. C.; Langworthy, O. R., and Cakrtova, M.: The Multiple Sclerosis Problem in Baltimore City, Am. J. Hyg. **35**:1, 1942.

3. Davidson, C. H.: Multiple Sclerosis, in Tice's Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1947, vol. 10, chap. 20, 1a. Bing, R., and Reese, H.: Die multiple Sklerose in der Nordwestschweiz, Schweiz. med. Wchnschr. **56**:30, 1926.

regularly each year. As a consequence, the remainder of the cohort for a given year diminishes as the period increases. The regular distribution of cases starting before 1939 can be explained by a constant withdrawal

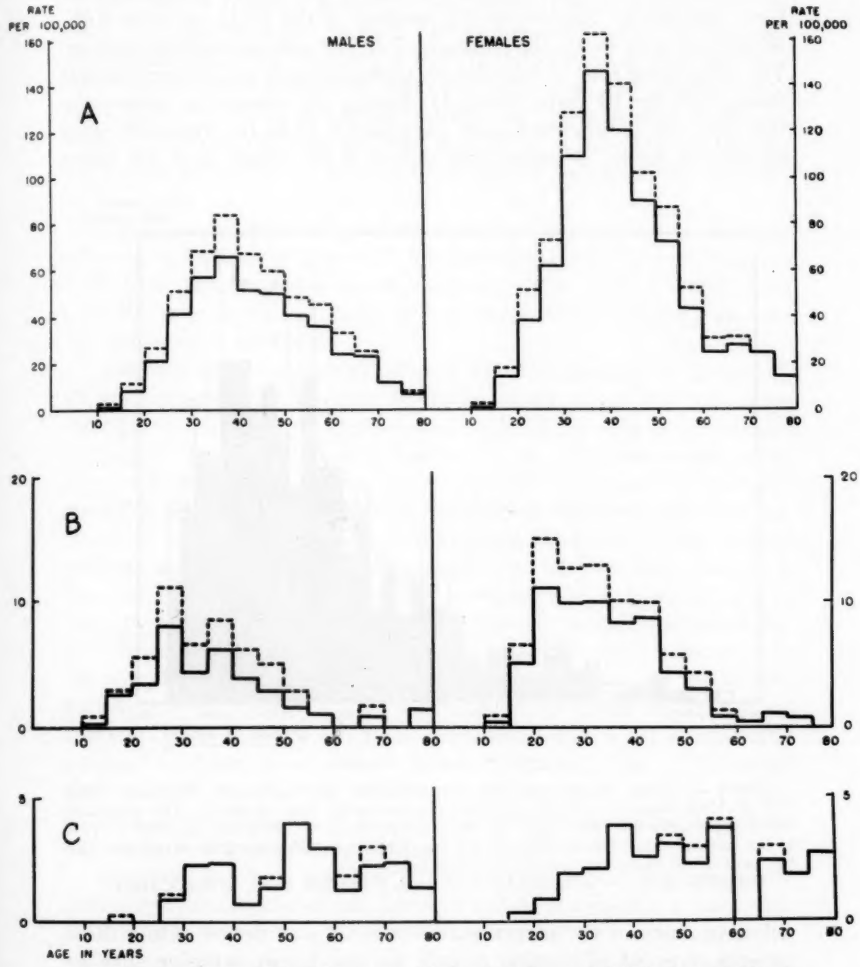

Chart 1.—Age-specific rates for multiple sclerosis per 100,000 of population in Boston and Brookline from 1939 to 1948, inclusive. *A*, prevalence (existing annual cases); *B*, incidence (new annual cases); *C*, mortality.

Possible and probable cases are indicated by the broken line; probable cases, by the solid line.

each year. The smoothed curve is computed under the assumption that the incidence was the same from 1907 to 1939 and that the rate

of disappearance was constant. The observed data are fitted to an annual incidence of 4.9 per 100,000 and an annual rate of disappearance of 12.8 per cent [4] in the years before 1939. In the 10 years after 1939, it was observed that 10.32 per cent of the annual prevalence disappeared or were withdrawn. Since only 3.0 per cent of the 10.32 per cent withdrawals were by death, the remaining 7.32 per cent requires explanation. The withdrawal rate, at least for the probable cases, was rather constant throughout the 10 years (table 3), leaving the reasonable assumption that only an unimportant part disappeared from the recorded cases because of death. Disappearance due to death would have left fewer

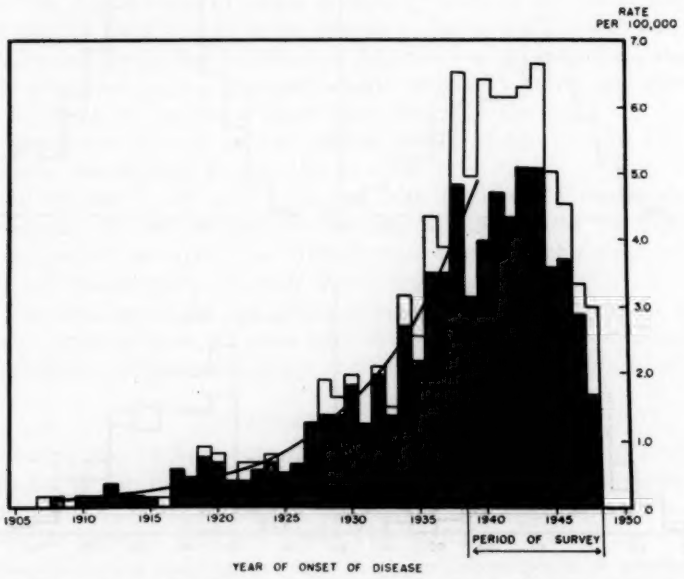

Chart 2.—Cases of multiple sclerosis recorded in Boston and Brookline from 1939 to 1948, showing rates per 100,000 population by year of onset. The smoothed curve represents the rates expected to be observed in the period from 1939 to 1948 if the annual rate of new cases is 4.9 per 100,000 in all preceding years and 12.8 per cent of all cases are withdrawn each year.

Probable cases are indicated by clear areas; probable cases, by black areas.

unknown cases in the earlier part of the 10 year period. Only three patients recorded in hospital records as "not known whether alive or not on Jan. 1, 1949" were later identified from death certificates.

4. If i is the annual incidence, 1907 to 1939, and r is the rate of withdrawal, then the number of patients remaining from the cohort with onset of disease t years before 1939 is

$$y = i e^{-rt}$$

from which i and r can be determined by regression analysis of the logarithmic form.

A more plausible reason for disappearance is emigration from the area. Seven per cent is a high, but not impossible, annual migration from a general population over a long period; it would mean that only 12 per cent of residents remain in the city of Boston for 30 years or more. It might well be, however, that patients suffering from multiple sclerosis tend to move from a large city. In such circumstances, the death rate from the disease would be higher in rural areas and smaller cities; but reported deaths from multiple sclerosis in Massachusetts, excluding Boston, 1939 to 1948, were 0.73 per 100,000, as against 0.96 for Boston. An excess emigration of patients from Boston cannot be demonstrated on this basis.

Finally, some of the withdrawals may be due to recovery. Multiple sclerosis is typically permanent. Complete remission for several years does occur, but relapse is almost inevitable. The constant withdrawals over 30 years cannot commonly be due to remissions requiring no subsequent medical attention.

The total cases of the series included a number grouped as "possible." Of the untraced withdrawals for the last 10 years, 40 per cent were from such cases, although they accounted for only 20 per cent of prevalence. In epidemiology, all cases of a disease, severe, slight and latent, enter into judgment of the full effect of a disease on a community. Tuberculin reactions reveal the full impact of tuberculosis, while clinical cases are no more than a fraction of all tuberculous infections. Only clinical methods can determine whether a patient has multiple sclerosis, and a diagnosis is supported principally by persistence of the disease. However, this limitation on observation should not exclude the possibility of a milder form of multiple sclerosis of more transient character than the typical form. Such mild forms could conceivably persist for shorter periods and be included in a survey, with their presence and disappearance explaining the relatively high withdrawal which is not satisfactorily ascribed to death or migration. Since withdrawals during the period 1907 to 1939 were of the same order of magnitude as during 1939 to 1948, it is justifiable to consider the occurrence of the disease to have been unchanged during the past 40 years.

Mortality has been considered thus far only as a factor influencing prevalence. Death in multiple sclerosis will be analyzed in a later publication, with attention to duration and severity at various ages of attack and to variations in the clinical nature of the disease as factors in longevity.

The data here presented have value for both clinical medicine and public health. The frequency of occurrence according to time, place and person is basic in guidance of epidemiological study of the natural history of a disease. The present study will find its full value when similar data are collected one or more decades from now and compared

with the current situation. Planning for care of persons with chronic disease in a community requires knowledge of the frequency of a disease. From the standpoint of clinical medicine, the days when something more may be offered than a clinical management directed only toward prolongation of life are clearly possible. Rational evaluation of new methods of treatment requires knowledge of existing life expectancy for the disease.

SUMMARY

Hospital records, practicing physicians and death certificates gave information on 783 patients with multiple sclerosis among residents of Boston and Brookline during the 10 year period 1939 to 1948. Hospitals yielded 62 per cent of cases; 34 per cent were obtained from physicians, and 4 per cent became known solely through death certificates.

Only one half of known deaths from multiple sclerosis were recorded by death certificates. One fourth of the cases revealed by death certificates were not among medical records of hospitals and private physicians.

The annual prevalence (existing cases during the year) of multiple sclerosis is between 43 and 51 per 100,000 population; the annual incidence rate (new cases) was between 3.9 and 5.4, and the mortality rate is between 1.4 and 1.5. The rates cited depend on whether or not cases classified as possible cases are included in the total.

The number of patients annually withdrawn from the Boston population by death or other cause is the essential equivalent of the new cases that develop. Deaths account for only 29 per cent of withdrawals, with the remainder due to emigration or recovery.

The computed incidence of multiple sclerosis in Boston gives rates that are fairly constant over the past 40 years. Rates per 100,000 females exceed those for males in the ratio of 1 to 1.74 for prevalence, 1 to 1.62 for incidence and 1 to 1.34 for deaths.

EFFECTS OF ACTH IN PATIENTS WITH MENTAL DISEASE

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THE POSSIBLE occurrence of disordered function of the adrenal cortex in patients with mental disease has interested workers in psychiatry for many years. Although no precise formulation of the nature or significance of changes in function of the adrenal cortex in such diseases has been or can be made, recent increases in knowledge of the function of that gland and of the action of steroid hormones have resulted in the accumulation of data bearing on this problem.

Severe hypoglycemia, convulsions induced by drugs or by electric shock, and fever cause changes in blood eosinophil and lymphocyte counts and in the urinary excretion of uric acid in patients with mental diseases, including schizophrenia, showing that the adrenal cortex responds to severe stress.[1] In addition, the milder stress of the effect

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1. (*a*) Gross, M.: Insuline et schizophrénie, Schweiz. med. Wchnschr. **66**:689, 1936. (*b*) Harris, A.: Cardiazol Treatment of Schizophrenia, J. Ment. Sc. **84**:735, 1938. (*c*) Mikkelsen, W. P., and Hutchens, T. T.: Lymphopenia Following Electrically Induced Convulsions in Male Psychotic Patients, Endocrinology **42**:394, 1948. (*d*) Parsons, E. H.; Gildea, E. F.; Ronzoni, E., and Hulbert, S. Z.: Comparative Lymphocytic and Biochemical Responses of Patients with Schizophrenia and Affective Disorders to Electroshock, Insulin Shock and Epinephrine, Am. J. Psychiat. **105**:573, 1949. (*e*) Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Leukocytes of Blood in Man After Electrically Induced Convulsions, Arch. Neurol. & Psychiat. **62**:624 (Nov.) 1949. (*f*) Altschule, M. D.; Parkhurst, B. H., and Tillotson, K. J.: Decreases in Blood Eosinophilic Leukocytes After Electrically Induced Convulsions, J. Clin. Endocrinol. **9**:440, 1949. (*g*) Altschule, M. D.; Altschule, L. H., and Tillotson, K. J.: Changes in Urinary Uric Acid–Creatinine Ratio After Electrically Induced Convulsions in Man, ibid. **9**:548, 1949. (*h*) Katzenelbogen, S.; Harms, H. E.; Williams, R.; Barkoff, S.; Brody, M. W., and Harpman, M.: The Insulin Treatment in Schizophrenic Patients: Clinical and Biochemical Studies, Am. J. Psychiat. **95**: 793, 1939. (*i*) Rees, L.: Physiological Concomitants of Electronarcosis, J. Ment. Sc. **95**:162, 1949. (*j*) Tsai, S. Y.; Bennett, A.; May, L. G., and Gregory, R. L., Effect of Insulin Hypoglycemia on Eosinophiles and Lymphocytes, of Psychotics, Proc. Soc. Exper., Biol. & Med. **74**:782, 1950.

of the injection of epinephrine results in normal responses of the adrenal cortex, as measured by changes in blood leukocytes, in patients with schizophrenia and other mental diseases.[2]

Thorn and associates [3] formulated a method for standardized testing of the responsiveness of the adrenal cortex to stimulation; this test involves measurement of changes in blood eosinophilic granulocytes and of urinary excretion of uric acid after the intramuscular injection of 25 mg. of pituitary adrenocorticotropic hormone (ACTH). Pincus, Hoagland and associates [4] carried out this test and made other studies on patients with schizophrenia; they concluded that the adrenal cortex does not respond normally to this stimulation in schizophrenia, although in a subsequent study they found that half of their schizophrenic patients did respond in a normal fashion.[5] Gildea and associates [6] also showed in a few patients that the response to ACTH, measured in the same way, was normal. In view of these discrepancies, it was decided to study again the effects of ACTH in patients with mental disease.

EFFECTS OF ACTH ON THE ADRENAL CORTEX FUNCTION OF PSYCHOTIC AND NONPSYCHOTIC PATIENTS

Blood Eosinophilic Granulocytes.—The injection intramuscularly of 25 mg. of ACTH resulted in a fall in blood eosinophils of between 60 and 95 per cent, measured as described elsewhere [1f]; other doses had similar effects. Diagnostic categories, duration of illness and presence or absence of psychosis apparently did not influence this response (table; chart 1).

Urinary Uric Acid–Creatinine Ratio.—The effect of the injection of ACTH was a variable increase in this ratio, measured as described elsewhere [1g]; no difference between psychotic and nonpsychotic patients was found (table; chart 1).

17-Ketosteroid Excretion.—One patient, whose 17-ketosteroid excretion was 14.0 and 12.0 mg., respectively, on two days before ACTH

2. Parsons, Gildea, Ronzoni and Hulbert.[1d] Altschule and others, to be published.

3. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: The Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005 (July 17) 1948; correction, ibid. **137**:1544 (Aug. 21) 1948.

4. Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, L. P.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. **11**:74, 1949.

5. Hoagland, H.; Callaway, E.; Elmadjian, F., and Pincus, G.: Adrenal Cortical Responsitivity of Psychotic Patients in Relation to Electroshock Treatments, Psychosom. Med. **12**:73, 1950.

6. Gildea, E. F., in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 553.

was started, received 100 mg. of the hormone a day. On the first day she excreted 10.4 mg.; on the second, 16.4 mg., and on the third, 15.5 mg., of 17-ketosteroids. Another patient, whose 17-ketosteroid excretion was 8.1 and 9.8 mg. on two days before ACTH was started, was given 560 mg. of the hormone in 17 days; on the thirteenth day she excreted 17.6 mg., and on the seventeenth day 15.0 mg., of 17-ketosteroids.

Sweat Sodium Concentration.—The injection of ACTH in the doses shown was followed by a decrease in sodium concentration in the urine and sweat which was at least normal in degree (table). It is to be

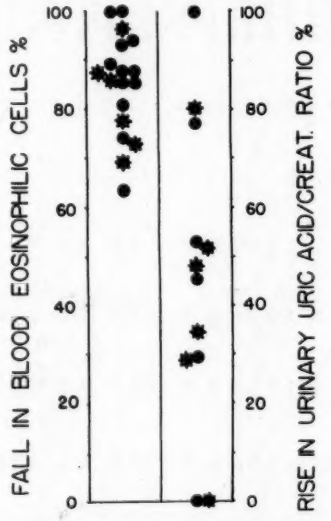

Chart 1.—Changes in blood eosinophil count and urinary uric acid-creatinine ratio four hours after the injection of 25 mg. of ACTH. Values for psychotic patients are shown by black circles; values for nonpsychotic subjects, by stars.

noted that the sweat sodium concentration may be elevated in untreated psychotic patients.[7]

Blood Sugar.—A. In one group of patients, most of them ill with schizophrenia for years or decades, the blood sugar was studied, using the Folin-Wu method,[8] before and again three hours after the admin-

7. Grunebaum, H., and Altschule, M. D.: Sodium Concentration of Thermal Sweat in Treated and Untreated Patients with Mental Disease, Arch. Neurol. & Psychiat. **63**:444 (March) 1950.

8. Folin, O., and Wu, H., cited by Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 456.

Case	Age	Sex	Dose of ACTH, Mg.*	Blood Eosinophils per Cu. Mm.		Urinary Uric Acid-Creatinine Ratio	Sweat Sodium, mEq.		Comment
				Before	Fall, %	Rise, %	Before	After	
Psychotic Patients									
St.	60	F	10	122	93	..	..	..	Manic-depressive, depressed, 5 mo.
Br.	39	F	25	156	86	..	68	58	Schizophrenia, 7 yr.; lobotomy 4 yr. before
			25	122	94	45	..	..	5 mo. later; no treatment
Ma.	47	F	25	244	81	..	..	..	Schizophrenia 18 yr.; lobotomy 5 yr. before
To.	54	F	25	59	74	..	..	..	Schizophrenia 23 yr.
Bu.	52	F	25	250	93	..	..	..	Schizophrenia 30 yr.
Em.	25	M	25	...	..	..	129	116	Schizophrenia 3 yr.
He.	57	F	25	59	63	100	..	..	Schizophrenia 7 yr.; lobotomy 1 yr. before
Be.	25	M	25	358	88	77	..	..	Schizophrenia 2 yr.; before treatment
			25	363	72	14	..	..	After 104 insulin treatments in 52 days
Da.	32	M	25	106	100	29	..	..	Manic-depressive, depressed, 1 yr.; before treatment
			25	84	96	0	..	..	After 111 insulin treatments in 49 days and 55 electric shocks in 154 days
Go.	24	M	25	225	80	..	..	..	Manic-depressive, manic, 1 wk.; before treatment
			25	484	70	50	..	..	After 51 insulin treatments in 23 days
Cu.	42	F	25	78	84	73	..	..	Manic-depressive, depressed, 4 mo.; before treatment
			25	147	94	0	..	..	After 72 insulin treatments in 47 days
Co.	52	F	25	87	85	0	..	..	Manic-depressive, depressed, 5 mo.; before treatment
			25	147	62	0	..	..	After 10 electric shocks in 30 days
Le.	37	F	50	263	90	..	..	..	Manic-depressive, depressed, 6 mo.
			50	113	89	..	..	..	2 days later
Dr.	51	M	100	213	77	..	89	80	Schizophrenia, 3 yr.
Ba.	47	M	100	156	70	..	58	49	Schizophrenia, 31 yr.
Nonpsychotic Patients									
Mu.	22	M	25	440	73	52	..	..	Psychoneurosis, mixed
Wo.	34	F	25	190	97	80	..	..	Psychoneurosis, mixed
Sw.	49	F	25	212	88	0	..	..	Psychoneurosis, reactive depression
Fo.	43	F	25	363	87	29	..	..	Psychoneurosis, reactive depression
Ri.	16	F	25	112	78	33	..	..	Psychoneurosis, compulsive-obsessive
Cm.	24	M	25	50	60	48	..	..	Psychoneurosis, reactive depression

* All ACTH used in these experiments was provided by Dr. John R. Mote, of The Armour Laboratories. A single batch of the hormone was used throughout, except in cases St and Le.

istration orally of 100 Gm. of dextrose. ACTH was then given twice a day for two or three days or longer. On the day chosen for study during the course of injections, ACTH was given at 8 a. m., and then 100 Gm. of dextrose was given by mouth at 9 a. m., blood being taken again for measurement of fasting sugar and three hours after the patient had ingested the dextrose. In all the patients the effect of ACTH was a striking increase in the blood sugar level three hours after the ingestion of dextrose, with less pronounced, inconstant changes in fasting levels (chart 2). It is evident that the ACTH caused a response

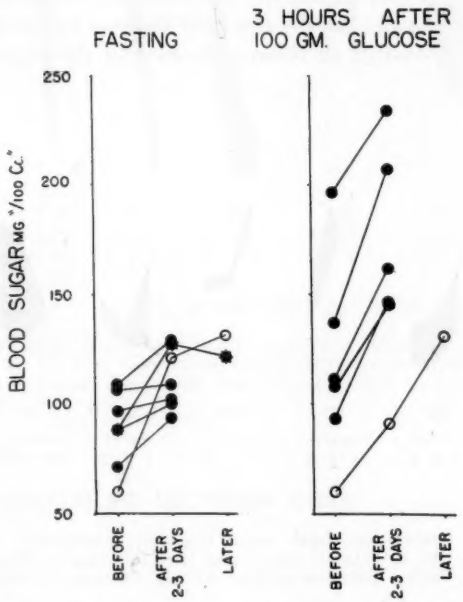

Chart 2.—Effect of ACTH, 25 mg. twice daily, on fasting blood sugar and on the blood sugar three hours after administration of 100 Gm. dextrose in psychotic patients.

in adrenal cortex function which resulted in a change in sugar metabolism. It is possible that the changes seen represent an abnormally great reaction, but since no normal subjects were studied by this method no such conclusion is warranted. Since this method was wasteful of ACTH, another plan was used.

B. Psychotic and neurotic patients were studied within a few days after their admission to the hospital. On one day, the blood sugar level was estimated before, and again at hourly intervals for three hours after, the ingestion of 100 Gm. of dextrose by the patient; a day or

two later a single injection of 25 mg. of ACTH was given at 8 a. m., followed an hour later by administration of 100 Gm. of dextrose by mouth, blood again being taken for estimation of the sugar level before and at hourly intervals for three hours after the dextrose was ingested. In three of the six nonpsychotic patients the injection of ACTH caused no significant change in the dextrose tolerance curve (chart 3). In one patient, case Fo, studied during an attack of migraine, retarded absorption of glucose from the intestinal tract occurred, as well as some degree of overreaction to ACTH; in two others, cases Mu and Cm, the degree of overreaction was less marked. The psychotic patients, some of whom initially had the abnormal dextrose tolerance curves seen commonly in psychosis, all showed elevation of the sugar curve when

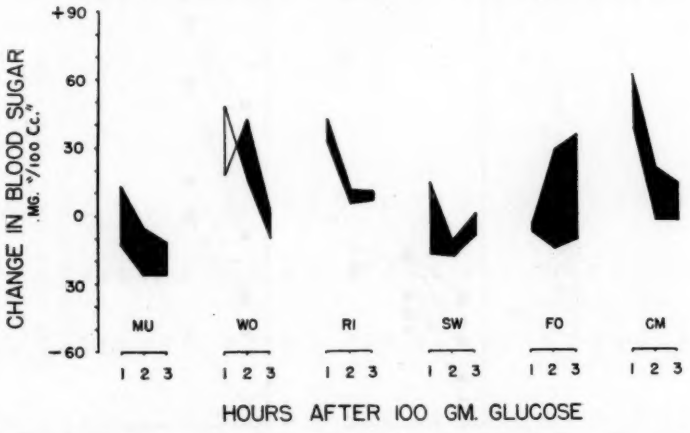

Chart 3.—Differences in blood sugar levels of nonpsychotic patients after ingestion of 100 Gm. of dextrose before and after injection of 25 mg. of ACTH. When values are higher with than without ACTH, the area is blacked in.

dextrose was given after a single injection of 25 mg. of ACTH (chart 4). It is evident that changes in carbohydrate metabolism occur in psychotic patients after injection of ACTH in this fashion; although the groups of patients studied were so small as to create the possibility that chance dictated the differences found in the psychotic and the nonpsychotic patients, it is possible that the metabolic response to the injection of ACTH is greater in psychotic than in nonpsychotic patients. That some patients with severe neurosis may show physiologically a change approaching that seen in psychotic patients is not surprising.

Effect of ACTH on Psychological Phenomena in Psychosis.—In recent months it has become clear that the injection of large amounts of ACTH or of cortisone (17-hydroxy-11-dehydrocorticosterone) may

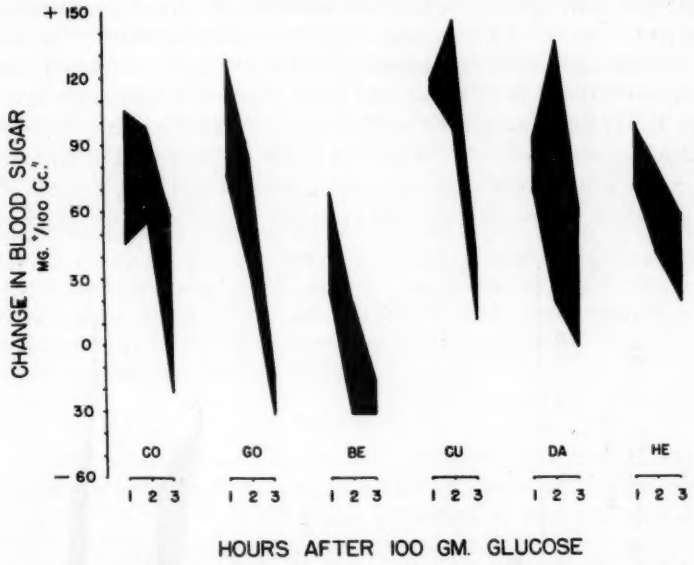

Chart 4. —Differences in blood sugar levels in untreated psychotic patients after ingestion of 100 Gm. of dextrose before and after injection of 25 mg. of ACTH. When values are higher with than without ACTH, the area is blacked in.

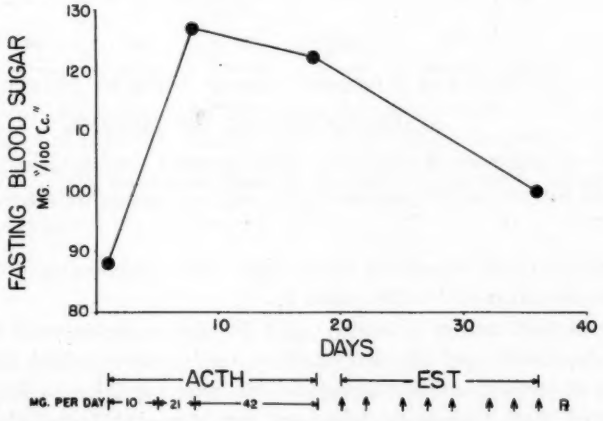

Chart 5.—Effects of ACTH and electric shock therapy on the fasting blood sugar level in a psychotic patient.

give rise to mental changes in persons previously normal mentally. More than two years ago, before this was known to us, certain considerations led to the use of ACTH in large amounts with two patients. The first, a woman aged 66 with manic-depressive psychosis, depressed type, received 570 mg. in 17 days; after a few days she became more active, and this change was deemed improvement. A few days later, however, hallucinations developed. At the end of the 18 day period of injections she was still extremely agitated and depressed and was, accordingly, given eight electric shocks, with complete remission of the psychosis

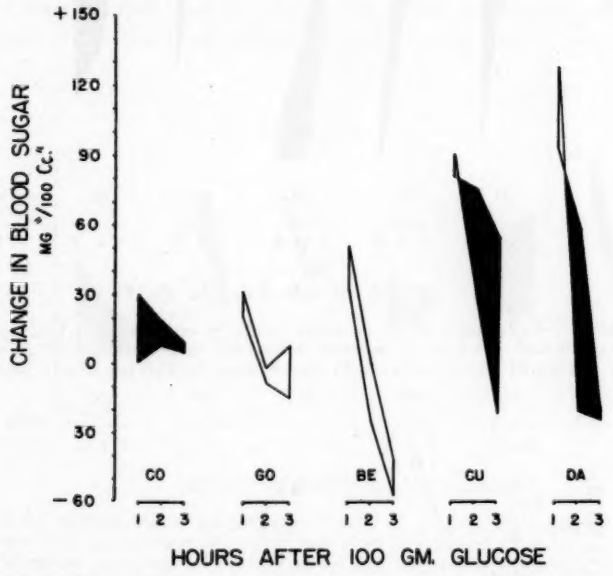

Chart 6.—Differences in blood sugar levels in treated psychotic patients after administration of 100 Gm. of dextrose by mouth before and after injection of 25 mg. of ACTH. When values are higher with than without ACTH, the area is blacked in.

and reversal of the changes in blood sugar which had developed during the administration of ACTH (chart 5).

The second patient, a woman, aged 39 with manic-depressive psychosis, depressed type, who was unable to receive electric shock therapy because of minimal active tuberculosis, the latter condition having been discovered after pulmonary lobectomy for stenosing bronchitis, was given a course of insulin therapy, without relief. After an interval she received 900 mg. of ACTH in 10 days; no improvement, and probably some worsening, in the depression occurred.

In addition, three of the patients in the present study who received ACTH for two or three days showed increased activity, with evidence of tension, restlessness and irritability.

Effects of Shock Therapy on Reaction to ACTH.—Some evidence of lessened responsiveness to ACTH after treatment, as measured by changes in blood eosinophils and urinary uric acid, was present in all five of the patients given insulin or electric shock therapy or both (table). The effect of ACTH on dextrose tolerance varied; one patient, case Cu, who was made worse by insulin therapy, showed a greater change after injection of ACTH than before (chart 6). Two others, cases Co and Da, who were slightly improved after electric shock, showed some lessening when studied after treatment; both relapsed within a week. Two others, cases Go and Be, who were improved and discharged after treatment, showed loss of the overreactivity to ACTH present on admission to the hospital.

COMMENT

It seems clear that in patients with schizophrenia or depression of any duration the reaction of the adrenal cortex to certain physical stresses and to the injection of ACTH is not diminished as compared with the changes observed in nonpsychotic subjects. It is possible, moreover, that psychotic patients show exaggerated metabolic changes after the injection of ACTH. If the latter observation should prove valid, it might be possible to relate psychosis to metabolic changes consequent to an unusual response of the adrenal cortex to ACTH or of the tissue to cortical hormone released during ordinary stresses.

CONCLUSIONS

Changes in eosinophil count, uric acid and 17-ketosteroid excretion and sweat sodium concentration after the injection of ACTH are not diminished in psychotic patients as compared with the changes in nonpsychotic subjects. Patients with schizophrenia or manic-depressive psychoses appear to show greater than normal changes in carbohydrate metabolism after the injection of ACTH.

EXPERIMENTAL STUDY OF A CASE OF INSENSITIVITY TO PAIN

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IT HAS been frequently observed that wide individual differences exist in what Wolff and Hardy [1] have called the reaction to pain. However, cases in which the usual behavioral and physiological responses to noxious stimuli are apparently totally absent are rare enough to have aroused considerable scientific interest. Many of these cases not only are characterized by absence of reaction to pain but, through verbal report, have led investigators to infer that the direct perceptual experience of usually painful stimuli is very different from normal.

Several cases have been reported in the scientific literature of the appearance of general cutaneous anesthesia in which pain sense has been involved along with touch, temperature and pressure sensations.[2] Circumscribed analgesias have been observed frequently. However, these examples of disturbances in pain sensitivity appear to be in a different category from the rare reports appearing later of cases of more specific lack of reaction to pain. Schilder and Stengel,[3] in a study of patients with lesions of the brain, reported having observed 10 cases of what they term "asymbolia for pain." This was described as a dulling of the appreciation of pain—a condition which was usually spread over

From the University of Saskatchewan, Department of Psychology.

This investigation was carried out in the Laboratory of Psychology, Allan Memorial Institute of Psychiatry, Montreal. Dr. R. B. Malmo, director of this laboratory, not only made the study possible by securing the cooperation of the subject, but throughout the work made provision for generous use of all experimental facilities.

1. Wolff, H. G., and Hardy, J. D.: On the Nature of Pain, Physiol. Rev. **27**:167-199, 1947.

2. (*a*) Berkeley, H. J.: Two Cases of General Cutaneous and Sensory Anaesthesia Without Psychical Implications, Brain **19**:440-464, 1891; (*b*) The Pathological Findings in a Case of General Cutaneous Anaesthesia Without Psychical Implications, ibid. **23**:110-138, 1900. (*c*) Burr, C. W.: Two Cases of General Anesthesia, Univ. M. Mag. (University of Pennsylvania) **13**:245-251, 1900-1901.

3. Schilder, P., and Stengel, E.: Asymbolia for Pain: Report of a Case, Arch. Neurol. & Psychiat. **25**:598 (March) 1931.

the whole body and was always associated with an incomplete and insufficient reaction to pain. In six of their cases typical sensory aphasia was also present. The nature of the cerebral damage observed at autopsy in three cases led the authors to conclude that a lesion in a particular region of the left parietal lobe (probably in the gyrus supramarginalis) was the basis of asymbolia for pain. Dearborn [4] gave the personal history of a man who did not experience, and could not recall having experienced, any pain except headache. Critchley [5] mentioned having examined a young man who had been referred to him by a physician because of his apparent insensitivity to pinprick and other painful stimuli. He also reported a similar case, which had been described by Weir Mitchell, of a legal friend of his who had never felt pain keenly at any time of his life, though he had once bitten off the end of his own finger after it had been crushed. This man had also undergone operations for lancing an abscess and bilateral removal of cataracts without anesthetic.

Ford and Wilkins [6] described the cases of three children, aged 7 to 9 years, who they believed did not have true analgesia, no absence of pain as a sensation, but, rather, a lack of reaction to pain—an indifference to pain. These children, in clinical tests of sensibility, could appreciate light touch and could distinguish between warm and cool test tubes and between the head and the point of a pin. Yet their reaction to noxious stimuli, such as deep pricking with a pin, squeezing the achilles tendon and pinching the skin, deviated strikingly from a normal behavioral reaction and showed the absence of psychogalvanic response. Their personal histories were replete with instances of indifference to damaging stimuli, with the qualification that in two cases some pain of visceral origin appeared to produce a reaction. Ford and Wilkins expressed the belief that this was a congenital developmental defect in neural mechanisms concerned with the reaction to pain and comparable to color blindness, congenital word blindness and congenital word deafness. More recently, Boyd and Nie,[7] in the case of a 7 year old girl, presented a history and clinical picture which appears very characteristic of this syndrome. Again, owing to indifference to noxious stimuli, which could produce cuts, bruises, burns and fracture dislocations, this patient had incurred numerous injuries, infections were frequent and the left leg and ankle were the seat of chronic osteomyelitis

4. Dearborn, G.: A Case of Congenital General Pure Analgesia, J. Nerv. & Ment. Dis. **75**:612-615, 1932.

5. Critchley, M.: Some Aspects of Pain, Brit. M. J. **4**:891-896, 1934.

6. Ford, F. R., and Wilkins, L.: Congenital Universal Insensitiveness to Pain, Bull. Johns Hopkins Hosp. **62**:448-466, 1938.

7. Boyd, D. A., Jr., and Nie, L. W.: Congenital Universal Indifference to Pain, Arch. Neurol. & Psychiat. **61**:402-412 (April) 1949.

without pain ever having been reported. Absence of verbal report of pain and overt behavioral response was noted clinically in response to noxious stimuli. Otherwise, neurological examination revealed a normal status, and the results of physical, laboratory and psychological examinations were essentially normal. These authors were inclined (like Schilder and Stengel) to consider this as a congenital structural defect in the postcentral area or (like Ford and Wilkins) to regard it as a congenital aphasia-like disturbance.

Kunkle and Chapman [8] reported a similar disturbance in the reaction to pain occurring in a man aged 25. In addition to the usual personal history and the results of common clinical tests for pain, they reported further data obtained with more recent technics, notably (1) the Hardy, Wolff and Goodell [9] technic for measurement of the cutaneous pain threshold; (2) the Lewis [10] test for the production of muscle pain, and (3) the production of "cold pain" from the immersion of a hand in water at 5 C. In all these tests the patient did not report any pain or show any overt reaction, though it is important to note that in the "cold pain" experiment a decided rise in both systolic and diastolic blood pressure was shown, as well as an increased heart rate. Except for Ford and Wilkins' [6] brief reference to the psychogalvanic response, this appears to be the first time in the study of such cases that the examination of response to noxious stimuli has been extended into the measurement of various well known physiological accompaniments to pain.

Previous reports of this disorder, as summarized above, have been comparatively rare, although they have appeared more frequently in recent years. In many of the earlier reports the patients showed evidence of such widespread neurological damage that the facts relevant to pain were inextricably mixed with a variety of sensory and motor disorders (Berkeley,[2a,b] Burr, [2c] Schilder and Stengel [3]). Others have presented no more than the personal history of their patients (Dearborn,[4] Critchley [5]). With the exception of Kunkle and Chapman's [8] study, these reports (Ford and Wilkins,[6] Boyd and Nie [7]) have been confined mostly to the presentation of a case history, together with clinical observations on the response made to common neurological tests in terms of overt behavior and verbal report. As a consequence, the picture presented by these studies has not been consistent enough to establish clearly the absence of response to noxious stimuli according to all of the following three criteria for pain sensitivity: (1) a verbal

8. Kunkle, E. C., and Chapman, W. P.: Insensitivity to Pain in Man, A. Research Nerv. & Ment. Dis., Proc. (1942) **23**:100-109, 1943.

9. Hardy, J. D.; Wolff, H. G., and Goodell, H.: The Pain Threshold in Man, A. Research Nerv. & Ment. Dis., Proc. (1942) **23**:1-15, 1943.

10. Lewis, T.: Pain, New York, The Macmillan Company, 1942.

report of painful experience; (2) overt behavioral reactions, such as wincing, withdrawal or restlessness, and (3) physiological responses, as seen in the blood pressure, heart rate and respiratory changes. The case reported here presented many advantages which were absent in earlier investigations: (1) The subject [11] was in a favorable age range, intelligent and willing to cooperate; (2) there was no evidence of widespread neurological or psychological deterioration, and (3) there was available an unusually large amount of reliable background data from hospital records, dating back to the time the subject was 21 months old. Consequently, there appeared to be an opportunity to establish more clearly the possibility of a human subject's exhibiting absence of pain according to all the criteria of response enumerated above. The implications of such a study to theories of the nature of pain appear to be far reaching. A case in which, from birth, a person exhibits a complete, universal indifference and lack of reaction to pain must be a remarkable instance of organic defect, the answer to which may give insight into the physiology and psychology of pain.

REPORT OF CASE

General History.—The subject was a woman aged 22, white and Canadian born of British ancestry. At the time of this investigation, in the summer of 1948, she had completed the second year of university study. She then joined a research group at the Allan Memorial Institute for summer employment as a general assistant in filing records and in correcting and administering psychological tests. It was also understood that, simultaneously with this other work, a study was to be made of her apparent analgesia—a project which received her full cooperation. Throughout this period she showed herself to be very capable and cooperative and displayed remarkable initiative in her work.

She was born by normal delivery of healthy, highly educated parents and had one brother, one year her junior. Her father, a physician, died when she was 11 years old, and her mother remarried about seven years later. Her early education started in a French nursery school and was accompanied with language lessons from a German governess. Later, she attended a city elementary school but received most of her secondary education in private boarding schools. Although during this period of schooling she was often in conflict with her mother, and her studies were frequently interrupted by illness, she appears to have progressed satisfactorily, making friends and entering into student activities. She appears to have been a highly excitable child, who, at an early age, resorted to pounding her nose and to biting her tongue and hands in response to frustration. Later adjustments were satisfactory, and she presents the picture of a slight, active, highly self-reliant person.

Medical History.—The childhood of the subject was particularly marked by frequent hospital admissions and by the very early discovery of her apparently complete indifference to common pain-producing stimuli. At the age of 21 months she was hospitalized for incision of a large, soft abscess over the occipital bone. The case history at the time notes that the child was not sensitive to pain. When 3 years old, she was admitted three times for treatment of osteomyelitis of the right

11. Throughout this report the patient exhibiting insensitivity to pain is referred to as the subject.

calcaneus. No complaint of pain or tenderness could be elicited from the patient. During the same year, a pinch graft operation was performed on the right leg, which had received a third degree burn when the child had knelt on a hot radiator to watch children playing in the street. At the age of 5 years she underwent tonsillectomy and adenoidectomy. In 1935 four hospitalizations occurred, one for a condition diagnosed as acute pyelitis, the other three for treatment of osteomyelitis at the lower end of the left femur. Notes in the hospital records repeatedly mention lack of sensitivity to pain, which is reported to have existed since birth. After 1935, the subject's progress was less interrupted, and no further hospitalization occurred until she was 17, when she spent six months in the hospital for treatment of spinal osteomyelitis and surgical treatment of a knee.

Interview Material.—Early in the study, interviews with the subject were held to complete information about her insensitivity to pain. The material obtained, together with incidents of her medical history, presents a consistent picture of a remarkable lack of response to noxious stimuli. The tip of the tongue was deformed from severe biting, which occurred during childhood. The hands, legs and feet showed multiple scars, which had been produced by cuts, bites and scratches, many of which were unnoticed. After a day on the beach she had to inspect her feet carefully for cuts. She claimed on many occasions to have received deep cuts from shells which she had not noted until this inspection. At no time had she ever reported any form of ache or pain, such as headache, earache, toothache, stomach ache or menstrual pain. The whole of her ordinary activities of living from birth had repeated, again and again, the same theme of tissue damage that had gone unnoticed or been looked on indifferently. Frostbites in winter were frequent. Burns from hot objects and from overlong exposure to the sun had also been numerous. Although no damage from burns had been as serious as the incident of kneeling on a hot radiator, nevertheless, she had had sunburn on the back of the legs which, going unnoticed and unprotected from clothing, had become infected. It is also interesting that she reported never having felt the sensation of itch. From her life in boarding schools and university she had had ample opportunity to observe the behavior of others in response to the itch from sunburn, measles, chickenpox and urticaria. She herself, often simultaneously with others, had experienced the same causes for itching; yet she had never felt any particularly different sensation or any occasion for behavior such as she observed in friends. It is interesting to note that Kunkle and Chapman [8] also reported the absence of itch in their patient.

The subject looked on this defect in pain sensitivity as an organic deviation quite beyond her knowledge or comprehension. At the time of the study she showed some reticence in telling friends of this deviation from normal but felt that a study of the anomaly could be interesting, worth while and worthy of her cooperation. There was evidence of a curiosity as to what feeling could produce the pronounced pain reaction she has observed in others. She also expressed the belief that to a large extent her sensitivity to painful stimuli was increasing. This belief, it appeared in interviews, was largely due to the greater success she had had in later years in avoiding serious tissue damage. Later evidence made it appear much more likely that this was due to more adult behavior patterns and to learning to use other cues as a warning of potentially damaging stimuli. The sensitivity to pain which she apparently lacked did not appear indispensable either for normal personality development or as a warning signal of potential tissue damage to the organism. Nevertheless, this defect, along with a pronounced susceptibility to cutaneous infection, had proved very inconvenient, dangerous and potentially fatal.

Neurologic Examination.[12]—This examination of the subject was made on July 10, 1948 by Dr. F. L. McNaughton, of the Montreal Neurological Institute. He reported as follows: "The cranial nerves are normal except for the following observations: In tests for the corneal reflex, there is occasionally a very slight movement of the eyelids when the cornea is touched, and it is difficult to be sure that this is not a reaction to an approaching and threatening object. With the ordinary method of testing, one would say that the corneal reflex is absent on both sides. The patient does feel very light touch on the conjunctiva, and possibly on the cornea as well. On her face and elsewhere on the body she can distinguish between the touch of the finger alone and the touch of the finger associated with pinprick. At first, she thought I was digging in with a finger nail and said that she simply felt something sticking into the skin but that she experienced no pain with it. The same is true when a hypodermic needle is inserted into the epidermis. She feels it penetrating the layers but experiences no pain. Supraorbital pressure with the finger causes no discomfort whatsoever. A stick can be inserted up through the nostrils without causing any discomfort or tendency to sneeze or withdraw. The same is true when the external auditory canals or the drum membrane is touched lightly with a stick. There is no tickling sensation from either nasal orifice. The gag reflex can be elicited only by stimulating low down on the posterior pharyngeal wall.

"There is fair muscular development and no localized wasting or weakness, and tests of coordination are well performed with either hand or arm.

"The deep reflexes are normally active and equal on the two sides. The abdominal reflexes are active and equal, and the plantar responses, while slight, seem to be flexor in type.

"Her ability to distinguish between touch alone and touch associated with pinprick has already been noted. There is no reaction to heavy pressure on the achilles tendon of either leg. She can appreciate even very weak vibration, as tested with a tuning fork. Position sense in the toes also seems perfectly normal.

"She is able to distinguish between hot and cold objects anywhere on the body surface, even when the difference between the two temperatures is not great.

"The ciliospinal reflex was tested, but no definite change was noted. There are frequent alterations in diameter of the pupil at all times.

"Summary: Examination does not reveal any evidence of organic neurological disease, such as syringomyelia. There are several bony deformities which have resulted from osteomyelitis. The lateral malleolus of the left leg is abnormally large, though she has never had osteomyelitis of this region, suggesting the possibility of a Charcot joint. However, there is no unusual mobility or crepitus of this joint. There are no trophic changes in the fingers or toes and no unusual scars or calluses on the feet. The remarkable feature is the complete absence of any experience of pain or of the usual reactions to it.

"Histamine Test: The subject was given 0.1 cc. of a 1:1,000 solution of histamine phosphate intravenously, producing slight taste sensation in the mouth, throbbing sensation and specks before the eyes. At the same time, there were increased pulse rate and throbbing of the arteries in the neck. Headache was not produced."

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12. Dr. F. L. McNaughton gave valuable advice in the study of this case; Mrs. Leila Ghent carried out the electroencephalographic examinations; Mrs. Joan E. Spindler and Miss Thelma Gordon administered and scored the psychologic tests, and Mr. David Bélanger and Mr. A. A. Smith gave essential technical cooperation and criticism.

Electroencephalographic Examination.—A routine electroencephalographic investigation was made, involving complete monopolar and bipolar coverage of the scalp and sphenoidal lead recording. No pathological wave forms were revealed.

Psychological Tests.—A general investigation of the intelligence status was made with Wechsler-Bellevue Intelligence Scale and the Wechsler Memory Scale. The personality structure was explored, using the Rorschach Test, the Thematic Apperception Test, the Cornell Index (form N 2) and McFarland and Seitz's Psychosomatic Inventory.

The results with the Wechsler-Bellevue scale indicate a person of "very superior" intellectual efficiency, with a verbal intelligence quotient of 119, a performance intelligence quotient of 132 and a full scale intelligence quotient of 128. No gross disturbance of function was noted, although the subject did less well on the verbal than on the performance section of the test—the reverse of the usual situation. Although the Wechsler Memory Scale quotient of 106 was undeniably lower than the level expected from the intelligence rating, the performance suggested lack of attention control rather than any primary impairment of memory. The personality tests did not reveal any gross personality disorder or characteristics which were considered relevant to the subject's unusual history of indifference to pain.

Threshold Measurements.—Investigation was made on the effect of thermal stimulation, using the Hardy-Wolff apparatus to obtain thresholds for warmth and pain. For the warmth threshold, a blackened surface of the volar aspect of the forearm was used as the test area. This area was placed directly against the 3.5 sq. cm. opening of the Hardy-Wolff apparatus, and the subject was blindfolded so that no light was visible. A series of stimulations of three seconds' duration spaced at 30 second intervals were then presented. These started at 0 watts and increased in steps of 25 watts until a point was reached at which the subject signified that the lamp was on. The threshold thus represents a point, expressed in terms of wattage input to the lamp, at which the subject first perceived warmth in the exposure area during a period of stimulation.

This judgment was found difficult to make in spite of its apparently simple nature. The onset of warmth is so gradual that the area between the point at which the subject is sure there is no stimulation and the point at which warmth is certainly felt is broad and diffuse. A group of 16 controls tested in this way showed an average of 113 watts, with a standard deviation of 25.0 watts. The average threshold for the subject obtained in nine widely spaced trials was 184 watts, with a standard deviation of 39.5 watts. There appears, thus, some evidence that the subject's threshold for warmth was moderately elevated.

Several attempts were made with the subject to measure the threshold for pain using the standard method described by Hardy, Wolff and Goodell.[9] At first it proved impossible to measure any threshold, as pain was never reported, although stimulus intensities sufficient to cause blistering were given. No behavioral reaction of head withdrawal or wincing was ever shown. This failure to give a verbal report of pain, which is used as the basis for the determination of threshold, is most unusual. Kunkle and Chapman,[8] however, reported the same thing occurring in their patient, although in some tests a slight pricking sensation was reported at high intensities. A similar report was occasionally obtained in the present case, seeming to indicate that there was some change in the quality of sensation as the temperature increased. If this was so, the necessary requirements for obtaining a Hardy-Wolff pain threshold appeared to be present. After repeated trials with the thermal stimulator, it appeared possible for the subject to report reliably a change from soft, diffuse warmth to a more localized, pricking sensation as the intensity of the lamp was increased.

Threshold measurements were then taken, using the blackened forehead as the test area. The average threshold obtained with the subject in 12 widely spaced trials was 295 watts, with a standard deviation of 20.2 watts. A group of 17 control subjects showed an average threshold of 263 watts, with a standard deviation of 27.4 watts. According to Andrews and Workman,[13] a linear relation holds between wattmeter readings and radiometer readings obtained by the standard technic. Hence it may be estimated that the threshold indicated by the subject was approximately 0.24 Gm. calory per second per square centimeter. It appears that some kind of threshold has been established for the subject which is only moderately elevated above the normal threshold for cutaneous pain.

To examine further the nature of this "pricking" threshold, it was decided to try the effect of ingestion of 0.6 Gm. of acetylsalicylic acid. The subject's normal threshold was taken in the usual way, and a value was obtained which agreed closely with previous measurements. At 10:00 a. m. 0.6 Gm. of acetylsalicylic acid was administered orally and the "pricking" threshold measured rapidly every 15 minutes until 12:15 p. m. This single trial resulted in the subject's reporting a lowering of threshold. The decrease started out gradually and in 1¾ hours after the time of ingestion reached a maximum of 52 per cent below the starting threshold. This pronounced drop in threshold is the reverse of the effect reported by Wolff, Hardy and Goodell.[14]

The most likely conclusion seems to be that the subject was deceived by the effect which acetylsalicylic acid is reported to have on the sensation of warmth. Wolff, Hardy and Goodell [14] stated: "After the administration of acetylsalicylic acid the subject, during successive threshold readings, became aware of a change in the character of the stimulus. The sensation of heat which preceded the onset of pain became relatively more intense and it was with surprise that no pain was experienced. The probable explanation of this phenomenon is that the threshold of heat is actually lowered by acetylsalicylic acid."

It is also quite possible that the subject's "pricking" threshold was not a true threshold. It may have been that at this point a change in the character of the heat sensation occurred which the subject, lacking the painful element for a criterion, selected as the basis for her judgments.

Muscle Ischemia.—In this test, the upper right arm was snugly encircled with the cuff of a standard clinical sphygmomanometer. After the cuff had been inflated to 250 mm. of mercury pressure, the subject was instructed to exercise the right arm by gripping a hand dynamometer at a rate of once a second. The grip suggested was a firm one of approximately 14 Kg. Under these conditions, the subject in four trials gripped the dynamometer 64, 79, 95 and 102 times, an average of 85 contractions performed in as many seconds. She reported no muscle ache or pain, or any change in the quality of sensation from arm muscles immediately after the cuff was deflated and circulation restored. Lewis [10] found, using similar methods, that pain had a remarkably consistent onset after 24 to 25 such contractions. This pain, in Lewis' experiment, rose rapidly in intensity until it forced arrest of the exercise at a point between 60 and 80 such contractions.

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13. Andrews, H. L., and Workman, W.: Pain Threshold Measurements in the Dog, J. Pharmacol & Exper. Therap. **73**:99-103, 1941.

14. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Measurement of the Effect on the Pain Threshold of Acetylsalicylic Acid, Acetanalid, Acetophenetidin, Aminopyrine, Ethyl Alcohol, Trichlorethylene, a Barbiturate, Quinine, Ergotamine Tartrate and Caffeine: Analysis of Their Relation to the Pain Experience, J. Clin. Investigation **20**:63-80, 1941.

Corneal Reflex.—The corneal reflexes were tested and found to be absent. It was easily possible to touch the cornea repeatedly and to draw the cotton point directly across the eye. The subject at no time experienced pain but reported a sensation resembling that of touch or contact.

EXPERIMENTAL STUDY

After this preliminary investigation, a series of experimental studies was begun aimed mainly at amplifying data on the physiological aspect of the response to noxious stimuli in cases of this kind. These studies may be separated into two main divisions. The first group consisted of a number of experiments using pain-producing stimuli, and the second group, of a variety of stimulating conditions of a non-noxious nature. The physiological responses to these varied stimuli were measured by continuous readings of the blood pressure, heart rate and respiration. At the same time, all relevant behavioral reactions were observed, and notes were taken of the subject's report of experience during the experimental period.

The continuous blood pressure records were obtained with a recording sphygmotonograph which has been described by Kurt Lange.[15] In all procedures, the cuff of this instrument was attached high to the left upper arm of the subject. The heart rate was recorded on one channel of an Offner electroencephalograph, using lead II of the standard electrocardiogram. The rate was then obtained simply by counting the number of beats over a known period. Respiration was recorded using a pneumograph attached to a tambour and pen which marked in the standard way on the electroencephalograph.

In the general plan, all experimental procedures were divided into three parts. During the first part, the subject was given instructions and prepared so that continuous readings could be taken of all three physiological measures. The second part was the main experimental section. In every case this started with a rest period, followed by the period of stimulation and concluded with a poststimulation period of rest. In the final part, the subject was asked to report on experiences during the experiment. Data obtained from the subject were set against the results obtained with groups of controls made up largely of graduate university students of both sexes in the same age range as the subject.

PROCEDURES

Experiment 1.—Effect of pain due to local cooling.

This experiment lasted 20 minutes, divided in the following way: 1. A rest period of eight minutes was given, during which respiration and the heart rate were recorded. The systolic blood pressure was recorded only during the last three minutes of this period. 2. After this, the right hand of the subject was immersed in a 3 liter breaker filled with ice and water at a temperature of 0 to 2 C. The subject was instructed to remain passive during the time when the hand was being immersed and to allow the experimenter to accomplish the necessary movement. This period of stimulation lasted eight minutes, at the end of which time the hand was removed

15. Lange, K.: A Recording Sphygmotonograph: A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man, Ann. Int. Med. **18**:367-383, 1943.

by the experimenter. The ice water covered the hand to just above the wrist and was stirred frequently. 3. The remaining four minutes formed an after-stimulation rest, during which all three physiologic measurements continued to be taken. This procedure was followed with the subject and with a group of nine controls—four females and five males. The subject had six trials in all, the systolic blood pressure being recorded five times, the diastolic pressure once, the heart rate twice and the respiration once.

Experiment 2.—Effect of pain due to local heating.

The same procedure was used as that in experiment 1, with the following changes: 1. The stimulus used was hot water kept at a temperature of 49 to 51 C. 2. The time of actual immersion in the water was reduced from eight to five minutes. All records were taken and scored in the same way. This procedure was followed with the subject in two trials and with a group of six controls—four males and two females.

Experiment 3.—Effect of pain due to electric shock.

In this experiment, a series of electric shocks was used as the stimulus. The shocks were obtained from an inductorium and were administered by pressing against the volar surface of the right forearm a small lucite® holder which contained two fine electrodes set about 2 mm. apart. The systolic blood pressure only was recorded during this test. The period of stimulation started with a shock administered to the forearm. After this initial shock the electrodes were pressed firmly against the skin every seven to eight seconds. The time of administering the shock was carefully controlled by the experimenter, who synchronized his application of the electrodes with a signal light which flashed every 7.5 seconds. Shocks were continued until 20 to 26 had been administered. Prestimulus and post-stimulus periods were recorded in the usual way. The same procedure was followed with the subject and with eight controls—five males and three females.

Experiment 4.—Effect of non-noxious stimuli.

The first test used in this experiment was developed at the Allan Memorial Institute for work with psychoneurotic patients. The subject was given the necessary instructions, followed by a rest period of 40 seconds, during which a pretest level of systolic blood pressure was obtained. The test proper then started, when a frame, showing six white circles against a black background, was flashed on a screen on the wall opposite the subject. These circles were of slightly varying diameter, with the identifying numbers 1 to 6 placed above them. The task was to call out to the examiner the number of the largest circle. In series 1, a sequence of 20 such frames was projected at the rate of one every five seconds. The subject was then presented the same sequence in series 2 at a rate of one every three seconds, and in series 3 at a rate of one every two seconds. The actual presentation of the frames, with the brief pause between series, took approximately six minutes, during which time the systolic blood pressure was recorded. The test consisted actually of a simple, but relatively fine, discrimination of size conducted under mildly stressful circumstances in that the subject was required to respond rapidly. Records were obtained from the subject and from a group of 14 controls.

The second test used was a mirror-drawing task in which the subject was to follow the outline of a printed circle. The subject was to draw the line first around the outside of the circumference and then inside, attempting to keep always a distance of 1 mm. from the printed circle. A rest period of 30 seconds was given at the beginning, during which the systolic blood pressure was recorded. Then followed an instruction period of 90 seconds, during which the subject was instructed as to the nature of the mirror-drawing task to be performed. The performance period then followed and was terminated as soon as the subject com-

pleted the task or reached the maximum time limit of three minutes. This procedure was followed with the subject and with a group of 17 controls.

In the third test the subject pulled a hand dynamometer at maximum grip until fatigue prevented further contraction. The dynamometer was gripped by the right hand, while the systolic pressure was being recorded from the left arm. Instructions were given the subject to pull as nearly as possible at a rate of once a second, until forced to stop from fatigue.

RESULTS

At no time, during any of the experiments using noxious stimuli, did the subject report a sensation or feeling which could be interpreted as a report of pain. Ache, unpleasantness, unbearableness or pain itself was never described. Consistent with this was the complete absence of any observable signs of painful experience. In all three experiments using noxious stimuli the subject exhibited striking behavioral com-

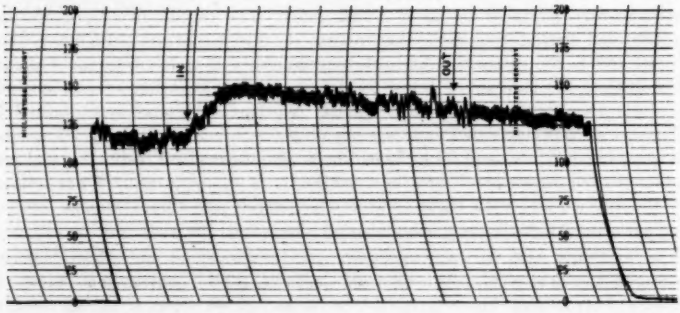

Fig. 1.—Record of systolic blood pressure taken on a control during experiment 1. *IN* marks the time of immersion of the right hand in water at 0 to 2 C.; *OUT* marks the time of withdrawal. Single spike systolic pressure readings are represented by the lower turning point of the systolic spike.

posure and unconcern. The normal, control subjects, on the other hand, never failed to report pain and showed many of the characteristic, overt behavioral reactions to intense pain. The "cold pain" was usually described as a dull, aching, crushing sensation which appeared shortly after the immersion of the hand in ice water and rose rapidly to a maximum, after which some decrease appeared to occur. This was accompanied with wincing, restlessness and frequent, partially executed withdrawals of the hand. It was also possible to observe pallor and sweating. Similarly, the hot water produced a report of pricking heat sensation, which rapidly became painful and resulted in wincing and withdrawal reactions. The electric shocks used in experiment 3 were also described by the controls as sharp, prickly and very unpleasant and were accompanied with apparently uncontrollable withdrawal movements.

This difference in report and behavior in response to noxious stimuli was associated with a marked separation of the subject from the controls in the results obtained from recording physiological changes. The greatest contrast obtained was in the blood pressure data from experiment 1. In figure 1 may be seen a typical systolic blood pressure record obtained from a control subject during this experiment. The rise in systolic pressure occurring immediately after the immersion of the hand in icewater is very apparent. This rise, however, is notably absent in figure 2, which shows the systolic pressure record of the subject during the same procedure. There were no exceptions to this differentiation of response. None of the nine controls failed to show a marked rise in blood pressure, whereas the subject did not show a rise in five trials, in which the systolic pressure was recorded, or in the sixth trial, in which diastolic pressure was measured. A clear idea of the whole effect of this experimental procedure on the systolic blood pres-

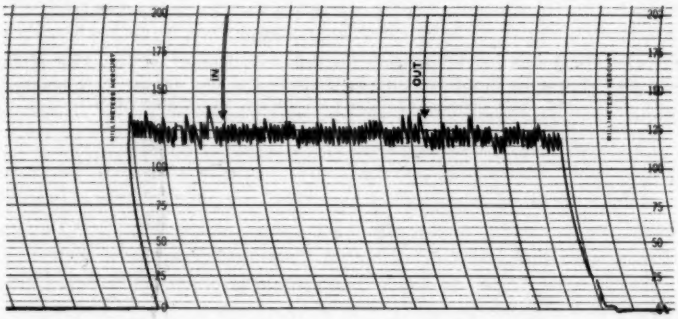

Fig. 2.—Record of systolic blood pressure taken on subject during experiment 1. *IN* marks time of immersion of the right hand in water at 0 to 2 C.; *OUT* marks time of withdrawal. Single spike systolic pressure readings are represented by the lower turning point of the systolic spike.

sure may be obtained by forming composite records for the controls and for the repeated trials on the subject. This was done by labeling the point of immersion of the hand on each record as 0 minutes and, with this constant point of reference, noting single spike readings for selected time points throughout the experiment. The sample spike readings at comparable time points were then averaged (1) for all the control records and (2) for the six repeated trials with the subject. The composite curves resulting from this analysis are shown in figure 3.

Figure 4 shows that immersion of the hand in water at 0 to 2 C. had a pronounced effect on the heart rate of the controls, which was not shown by the subject of this report. Heart rate readings were taken from the continuous record by selecting a 10 second sample every 30 seconds throughout the record. The number of beats in this 10 sec-

ond period was then counted and multiplied by 6 to give the heart rate expressed in the standard units of beats per minute. Time periods were made comparable from record to record by labeling the point of

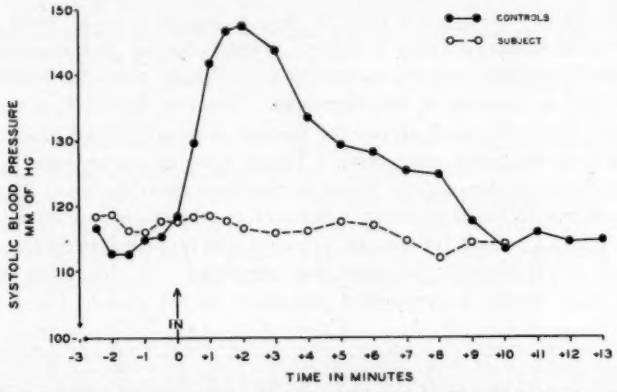

Fig. 3.—Composite curves showing the differential effect of pain due to local cooling on the systolic blood pressure of controls and the subject. *IN* marks the time at which the right hand was immersed in ice and water at 0 to 2 C.

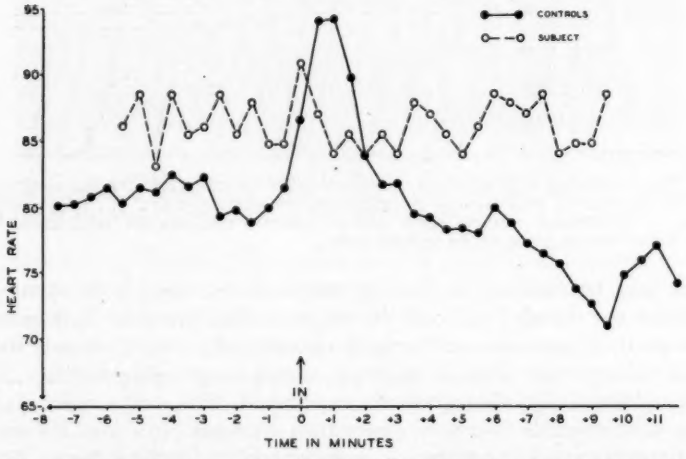

Fig. 4.—Composite curves showing the differential effect of pain due to local cooling on the heart rate of controls and the subject. *IN* marks the time at which the right hand was immersed in ice and water at 0 to 2 C.

immersion as 0 minutes and measuring all times from this fixed point of reference. Thus, the values from all the records could be combined by averaging rates which were at equal time units from 0. When this was done for the controls, the resultant composite curve (fig. 4) shows

an immediate rise in heart rate at the time of immersion which lasts about two minutes and then is gradually replaced by a marked retardation. The composite curve for two trials with the subject fails to show either of these reactions.

Again, there were no exceptions, as no control failed to show either a marked acceleration or a marked retardation, while the subject showed only random variations. The variability in heart rate of the subject during the whole course of the experiment was also much less than that of any control. When the standard deviation of all the heart rate readings on each individual subject is determined, it is apparent that the subject was the lowest of all—2.30 and 2.75 in two trials, as against the standard deviations for the control subjects, ranging from 3.63 to 14.9.

The chief difference between the subject and the controls in respiration occurred in the degree of disturbance in the pattern of breathing as a result of stimulation. A measure of this disturbance was obtained by dividing the whole pneumographic record into 30 second intervals and then looking at the pattern of breathing in each period. If there were irregularities in amplitude during any 30 second period, it was rated plus; if not, it was labeled minus. The percentage of respiratory irregularity, for the control group and for the subject, was then obtained by calculating what percentage of the total number of respiratory periods scored had been graded plus. The controls, as a group, showed a per cent respiratory irregularity index of 9 before stimulation and a rise to 41 while the hand was immersed in ice water. The subject showed a per cent respiratory irregularity index of 17 before stimulation and an actual drop to 10 during stimulation.

The hot water, used in experiment 2, as the pain-producing stimulus, did not prove entirely satisfactory. It was found difficult to control the temperature in such a way that pain was unmistakably experienced by the normal subject without its being so sharp and severe that withdrawal was forced. Nevertheless, when the data are treated in the same way, the results are consistent with those observed in experiment 1. Every control subject showed a rise in systolic blood pressure, which took place immediately after immersion of the hand. The average elevation for the control group amounted to 10.3 mm. of mercury. The subject showed no rise in systolic pressure in either of two trials. Similarly, the control subjects showed an average increase in heart rate of approximately 8 beats per minute. This occurred almost immediately after immersion of the hand and persisted until its withdrawal from the water. The subject showed no acceleration of heart rate at the time of immersion, though some rise was indicated later in the stimulation period. Individual heart rate records of the controls, however, failed to show a complete separation from those of the subject. In the

respiratory measure, the control group showed a per cent respiratory irregularity index of 5 before stimulation, with a rise to 29 while the hand was immersed in hot water. The subject showed a per cent respiratory irregularity index of 6 before stimulation and of 7 during stimulation.

In experiment 3, the only measure used was that of the systolic blood pressure. Again, a striking difference was noted between the controls and the subject which was consistent with the difference observed in overt behavioral reaction. Each control subject showed a rise in systolic blood pressure during stimulation. For the group, the average prestimulation systolic pressure was 122.2 mm., which rose to 141.3 mm. during stimulation—an average rise of 19.1 mm. The subject's average prestimulation level was 118.6 mm. During stimulation this rose 1.3 mm., to the average level of 119.9 mm.

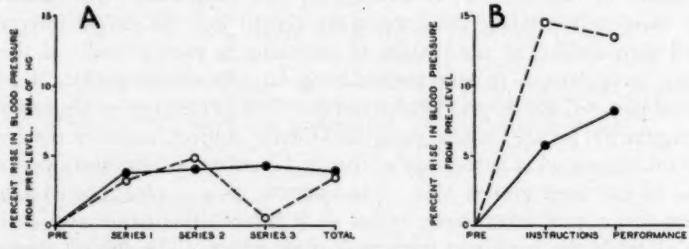

Fig. 5.—Curves showing the effect of (*A*) the perceptual test and (*B*) the katoptographic test on the systolic blood pressure of controls (solid line) and the subject (broken line).

Experiment 4 was introduced to eliminate the possibility that the subject's lack of vasomotor responses shown in the above results was general and might be shown under any stimulating conditions, noxious or otherwise. The first two tests of this experiment were known as the perceptual and katoptograph tests respectively and are so labeled in figure 5 *A* and *B*. In both tests, the systolic blood pressure levels for each period were obtained by averaging the values for all the individual spikes on the record during the relevant period. The results (fig. 5 *A* and *B*) indicate that the blood pressure responses of the subject associated with these experimental procedures follow closely those of the average for the control group. In the katoptograph test (fig. 5 *B*) the actual amount of change in systolic blood pressure for the subject was greater than the average for the controls. In the third test the subject gripped the dynamometer 240 times over a period of four minutes. This exercise produced a gradual steady rise in blood pressure, up to a maximum elevation of 22 mm. of mercury.

COMMENT

The results of the experimental work show on the part of the subject a remarkable absence of response to common pain-producing stimuli. This is true whether we consider the response in terms of (1) verbal report of painful feelings; (2) overt behavioral signs, such as wincing, vocal expressions and withdrawal, or (3) physiological response, as seen in the blood pressure, heart rate or respiratory measures. Although the application of stimuli, such as pinprick, cutaneous shock or heat, which are adequate for the production of pain in normal subjects, does produce the report of a pricking or sharp quality, this quality is never described as a painful experience by the subject. It is also unaccompanied with the usual overt reactions or associated physiological changes. These experimental findings are entirely consistent with the picture presented in the case history. Their special interest lies in the way in which they complete this picture by demonstrating the lack of physiological response to noxious stimuli in all measures used.

This absence of physiological response on the part of the subject is a significant finding which appears in striking contrast to the response shown by control subjects. These results with control groups may be supplemented by ample evidence from the literature. Nafe and Wagoner,[16] with both hot water (45 to 58 C.) and faradic stimulation, noted that the normal response was consistently one of verbal report of pain, associated with vasoconstriction and rise in blood pressure. Hines and Brown [17] showed the rise in blood pressure, due to immersion of a hand in water at 4 to 5 C., to be the normal response for a group of 87 controls. Seventy-six patients with symptoms of hypertensive vascular disease also showed a rise in blood pressure which was greater than that of their control group.

In the insensitivity to pain shown by the hysterical patient, such physiologic responses as the "cold pressor" effect have not been absent, though the experience of pain was denied. Cable and Smirk [18] packed ice around the arm of a patient showing symptoms of hysterical anesthesia. Although the patient denied experiencing pain, a rise in blood pressure of 17 mm. systolic and 11 mm. diastolic was shown. The patient of Kunkle and Chapman,[8] who they believed was not hysterical, nevertheless showed a marked cold pressor reaction without reporting pain. The

16. (*a*) Nafe, J. P., and Wagoner, K. S.: The Effect of Pain upon Peripheral Blood Volume, Am. J. Psychol. **51**:118-126, 1938; (*b*) The Effect of Pain upon Systemic Arterial Blood Pressure, ibid. **51**:390-397, 1938.

17. Hines, E. A., and Brown, J. E.: A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State, Ann. Int. Med. **7**:209, 1933.

18. Cable, J. W., and Smirk, F. H.: Blood-Pressure-Raising Reflexes in Hysterical Anaesthesia, Brit. M. J. **4**:874-875, 1941.

authors suggested that, since at least this part of the reaction to pain appeared to be present, the defect must lie at a sufficiently high level to allow such a reflex response to occur without, at the same time, pain being perceived. The special significance of the present report is that the subject appears to fall into a different category from the patients of either Kunkle and Chapman or Cable and Smirk. It must also be emphasized that this unique absence of physiological response appears specific to pain-producing stimuli. Certainly, normal vasomotor responses can be elicited in this subject, as was shown in the experimental results when non-noxious stimuli of a mildly stressful nature and exercise were used.

Examination of the data presented in this case, with a view to forming hypotheses concerning the nature of the anomaly, leads to many possible considerations. However, much of the evidence points to the location of the defect on an organic level. In this case the lack of response to noxious stimuli has been evident since birth and has been marked by a pervasiveness and consistency unusual in cases of psychological disturbance. The psychological examination and interviews, conducted over a period of three months, failed to show any evidence of a disorder which could plausibly result in this picture. Perhaps the most convincing aspect of the data appears in the absence of physiological response which accompanies the subject's denial of pain.

After this study was completed, Feindel [19] was able to make a histological study of the peripheral cutaneous innervation in this subject. He has indicated that the skin stained supravitally with methylene blue shows fine free terminals and networks in the superficial layers of the skin characteristic of the structures in normal subjects. Further studies have been undertaken with silver staining methods, the results appearing to indicate that the peripheral innervation differs little from that found in normal biopsies.

It appears that the problem is gradually narrowing down in the investigation of this peculiar disorder. 1. There has been an increase in reports of such cases. 2. There has been gradual extension of the evidence that pain may be absent not only in terms of behavioral reaction and verbal report, but also in basic physiological accompaniments of intense pain. 3. Feindel's observations represent the first histological study in such a case and a further step in closing the gap. It would seem that future studies of this anomaly could quickly establish the absence of pain and focus attention on the elaboration of the precise location or nature of this disorder, which may be crucial to the understanding of pain.

19. Feindel, W. H.: Personal communication to the author.

SUMMARY AND CONCLUSIONS

The case is presented of a woman who from birth has shown a marked insensitivity to pain. In the introductory approach to this case, the main features are dealt with under the headings: (1) general history, (2) medical history, (3) interview material, (4) neurological examination, (5) electroencephalographic examination and (6) psychological tests.

This preliminary investigation reveals a history of a consistent lack of response to pain. Neurological examination showed no evidence of organic neurological disease, such as syringomyelia, and indicated a defect which appears specific to pain. This examination also revealed the absence of the corneal reflex in both eyes. Psychological tests showed superior intelligence (Wechsler-Bellevue intelligence quotient, 128). No pronounced personality disorders appeared. The electroencephalographic examination revealed no pathological wave forms. Evidence is given that the threshold for warmth in the subject is moderately elevated. Exploratory trials with the Hardy-Wolff thermal stimulator showed that the subject reported some of the pricking quality of heat without showing any reaction of pain, even at high intensities. It has also been noted that other "pricking" sensations are reported, such as commonly result from application of a pin or electric shock from an inductorium.

The most significant findings appear in the experimental results, which showed complete absence of physiological response to noxious stimuli in all measures used. These measures included recordings of blood pressure, heart rate and respiration, taken during two types of experiments, (1) those using noxious stimuli, and (2) those using non-noxious stimuli. In the first type, cold water at a temperature of 0 to 2 C., hot water at a temperature of 49 to 51 C. and electric shock from an inductorium were used as pain-producing stimuli. In the second type, a size discrimination test carried out under pressure of time, a mirror-drawing task and exercise with a hand dynamometer were used. Records of physiological response were supplemented by noting the verbal report of the subject and by observation of overt behavior. The same procedures were followed with a group of control subjects.

The results show absence of pain on the part of the subject according to all three criteria of (1) report, (2) overt reaction and (3) changes in blood pressure, heart rate or respiration. The response to noxious stimuli shown by the control groups, differentiates them, without exception, from the subject. On the other hand, the subject reacted like the control groups to the nonpainful types of stimulating conditions.

COLLOIDAL GOLD REACTION IN MULTIPLE SCLEROSIS

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MULTIPLE sclerosis is a not uncommon disorder of the central nervous system. Although characteristic pathologic changes have been demonstrated, the cause is unknown, and there is as yet no really adequate treatment.

The onset may be gradual or sudden; the course, acute, chronic, remissive or progressive. Because of the multiplicity of lesions, the clinical manifestations are extremely variable. Obviously, such a disorder may be simulated by, or may simulate, various other conditions. Indeed, it has been proposed that it is not an entity but is in reality a syndrome that may be produced by various pathologic processes. The diagnosis is made readily, and usually erroneously, by casual consideration, or more correctly by the painstaking process of exclusion. In such a situation any laboratory aid is welcome.

There is as yet no test specific for multiple sclerosis. Nonspecific alterations in the cell count, protein concentration and/or colloidal gold reaction of the cerebrospinal fluid have been reported in about 87 per cent of cases.[1] In those cases in which syphilis of the central nervous

This investigation was supported in part by a grant from the National Multiple Sclerosis Society.

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1. Freeman, D. A., and Merritt, H. H.: The Cerebrospinal Fluid in Multiple Sclerosis, A. Research Nerv. & Ment. Dis. Proc. (1949) **28**:428, 1950.

system can be excluded, the presence of a so-called first or second zone curve in the reaction of the spinal fluid to the colloidal gold test as commonly performed is contributory evidence of multiple sclerosis; however, these curves occur in no more than 25 per cent of cases of multiple sclerosis.[1]

The newer, quantitatively standardized colloidal gold test as performed under the supervision of Dr. Carl Lange in the Division of Laboratories and Research of the New York State Department of Health, has been shown by us in a preliminary study of 100 cases of multiple sclerosis to be of considerable value in the diagnosis of this disease.[2] This work has been continued and is the subject of the present report.

The mechanism of the colloidal gold reaction is not yet known, but the reaction is believed to be due to the presence of gamma globulins or similar substances in the spinal fluid acting as coagulators, on the one hand,[3] and of other substances, especially albumin, acting as protectors of the sol. Whether or not the presence of coagulating substances is due directly to parenchymal changes in the central nervous system [4] or is an indirect manifestation of degeneration is open to question. Kabat stated the belief that there may also be selective transudation through the blood-brain barrier.[5] He demonstrated a relative elevation of the gamma globulin of the spinal fluid in 85 per cent of his patients with multiple sclerosis. As this increase also occurs in other disorders, it, too, is not specific for multiple sclerosis.

METHOD AND MATERIAL

The quantitative colloidal gold test as performed in the laboratories of the New York State Department of Health is a perfected procedure differing in both technic and interpretation from the commonly used modifications of the original Lange

2. Von Storch, T. J. C.; Harris, A. H., and Lawyer, T., Jr.: Cerebrospinal Fluid Examination in Diagnosis of Multiple Sclerosis, New York State J. Med. **49**:2145, 1949.

3. Kabat, E. A.; Moore, D. A., and Landow, H.: An Electrophoretic Study of the Protein Components in Cerebrospinal Fluid and Their Relationship to the Serum Proteins, J. Clin. Investigation **21**:571, 1942. Lange, C.: Theory of the Colloidal Gold Reaction: Reactions Between Gold Sol and Isolated Protein Fractions, J. Lab. & Clin. Med. **30**:1006, 1945.

4. (*a*) Thompson, L. J.: Interpretation of the "Paretic Curve" in Lange's Colloidal Gold Test, Arch. Neurol. & Psychiat. **5**:131 (Feb.) 1921. (*b*) Lange, C., and Harris, A. H.: The Degenerative Syndrome, to be published.

5. Kabat, E. A.; Freeman, D. A.; Murray, J. P., and Knaub, V.: A Study of the Crystalline Albumin, Gamma Globulin and Total Protein in the Cerebrospinal Fluid of 100 Cases of Multiple Sclerosis and Other Diseases, Am. J. M. Sc. **219**:55, 1950.

colloidal gold test.[6] The procedure requires considerable care in performance and experience in interpretation. The technic has been described in several publications.[7] (Information relative to any recent alteration of details may be obtained by communicating with the Division of Laboratories and Research in Albany.) An outline of the essential features of performance and interpretation follows.

Stabilized citrated gold sol is added to the cerebrospinal fluid diluted in phosphate buffer.[7c] The usual series of 10 dilutions is compressed into the range of 1:15 to 1:576 (instead of 1:10 to 1:5,280, as in the original test). In the shorter range of dilutions the reaction of coagulators and protectors of the sol is more pronounced than in the higher dilutions (chart 1). The development of a stable, sensitive gold sol,[7b] a quantitative color standard[8] and satisfactory controls, including a test fluid,[9] has permitted the performance of a test that is reproducible within fairly narrow limits of error. Since much finer distinctions of color can now be made than with the original colloidal gold reaction, and since these distinctions have a certain degree of significance, the use of a finer color scale, 0 to 20, instead of the 0 to 5

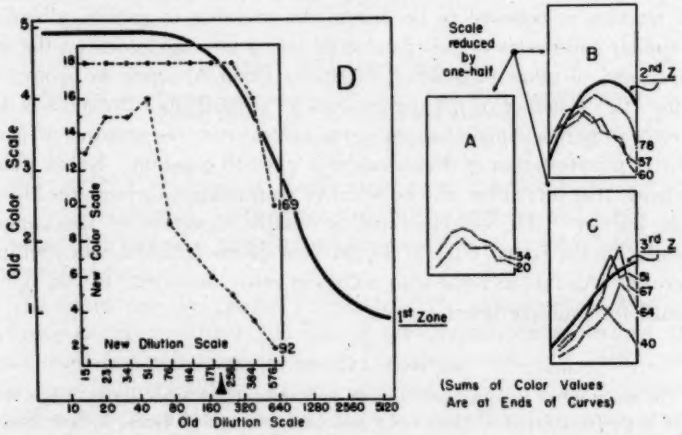

Chart 1.—Comparison of characteristic examples of the "new" quantitative colloidal gold reaction and the "old" (routine) colloidal gold reaction.

6. Lange, C.: Die Ausflockung kolloidalen Goldes durch Zerebrospinalflüssigkeit bei luetischen Affektionen des Zentralnervensystems, Ztschr. f. Chemotherap. 1:44, 1912.

7. (*a*) New York State Department of Health: Standard Methods of the Division of Laboratories and Research of the New York State Department of Health, ed. 3, Baltimore, Williams & Wilkins Company, 1947, p. 361. (*b*) Lange, C., and Harris, A. H.: Stabilized Citrate Gold Sol for Use in the Colloidal Gold Reaction, J. Ven. Dis. Inform. **29**:265, 1948; (*c*) The Significance of the p_H in the Gold Reaction, J. Lab. & Clin. Med. **29**:970, 1944.

8. Lange, C.; Miller, J. K., and Harris, A. H.: Simplification of the Colloidal Gold Test of Cerebrospinal Fluid Based on Quantitative Standardization, Am. J. Clin. Path., to be published.

9. Lange, C.: A Test Fluid for Control of the Gold Reaction, J. Lab. & Clin. Med. **32**:579, 1947.

of the old test, has been adopted. The test is so adjusted that normal cerebrospinal fluids elicit a curve, designated as type A, that is consistent in shape; the location of the maximum reaction is in the tube containing fluid diluted 1 : 51 or 1 : 76, and the sum total of the color values (based on the color scale 0 to 20) in the 10 tubes of the series is less than 40. The type B curve is characterized by a maximum reaction in the tube containing fluid diluted 1 : 51, 1 : 76 or 1 : 114, and the sum is 60 or more. These type B curves are of variable significance. Curves with the shape of type B but with the sum total in the border zone between 40 and 60 are classified as type A/B curves. Such curves may or may not be associated with significant pathologic processes. The type C curve is characterized by a relatively slight degree of coagulation in the first tube, gradually rising to a maximum which is occasionally in the 1 : 114 dilution, but oftener in the 1 : 171 dilution or higher, with a considerable degree of coagulation in the tubes following. Significant departures from this characteristic shape of the type C curve call for different designations,

TABLE 1.—*Types of the Colloidal Gold Reaction in Definite and Probable Cases of Multiple Sclerosis and in Other Diseases of the Central Nervous System*

	Type D Colloidal Gold Reaction*									Other Types of Colloidal Gold Reaction								
	Strong			Weak or Minimal			All Forms									All Forms		
Disorder	No.	% Multiple Sclerosis	of D Reaction	No.	% Multiple Sclerosis	of D Reaction	No.	% Multiple Sclerosis	of D Reaction	C/D	C	B/C	B	A/B	A	No.	% Multiple Sclerosis	Total Cases of Multiple Sclerosis
Definite multiple sclerosis.	86	(54)	[33]	63	40	24	149	(94)	[57]	1	0	0	3	4	1	9	(6)	158
Probable multiple sclerosis.	8	(18)	[3]	12	26	4	20	(44)	[7]	6	1	0	4	8	6	25	(56)	45
Total multiple sclerosis ..	94	(46)	[36]	75	37	28	169	(83)	[64]	7	1	0	7	12	7	34	(17)	203
Total non-multiple sclerosis	20	..	[8]	74	..	28	94	..	[36]									
Total D curves reactions	114			149			263											

* The figures in parentheses are assembled for visual comparison with chart 2; those in brackets, for comparison with chart 3.

such as the B/C or the C/D curve, depending on the elements involved in the shape of the curve. The type C curve is indicative of a definite abnormality in the cerebrospinal fluid. It occurs frequently in cases of compression syndrome, meningitis, encephalitis and bloody spinal fluid (of whatever cause).

The type D curve, with which we are specially concerned, is characterized by a plateau or by relatively high coagulation in the lower dilutions, at the left end of the curve. These forms may be divided into D (or strong D), weak D, and minimal D reaction curves, according to the extent of shift to the left, the location of the maximum coagulation zone and the total of the color values, ranging from 180 to 40, or even less.

Designation of color values is best accomplished with the unaided eye, as it entails integration of both color and degree of coagulation. Some practice in reading the color value is required. Even more experience is necessary in interpreting the curves. The results have seemed reasonably consistent. This study is based on the interpretation of the colloidal gold reaction as reported by the State Laboratory.

During the 18 month period from January 1948 through July 1949, a total of 10,362 samples of cerebrospinal fluid were examined in the laboratory at Albany.

Of these, the results of 3,169 were excluded because of contamination, insufficient information, patently unreliable sources, obvious purulent meningitis and any evidence of syphilis. The remaining 7,166 reports were subjected to more searching scrutiny, and from them were selected *(a)* all those in which there occurred type D curves not associated with syphilis, and *(b)* all those in which there was a stated diagnosis or reasonable suspicion of multiple sclerosis. These two groups were further investigated by examination of the patient, a review of the original medical record or, in a minority of instances, an evaluation of the situation from reliable information submitted to us by the patient's physician.

The diagnosis of multiple sclerosis was based on the history and examination. The cerebrospinal fluid was not considered in this evaluation except as it indicated syphilis, meningitis, subarachnoid bleeding or complete spinal cord block. Three factors were stressed in arriving at a diagnosis: a history of remission, multiplicity of lesions and exclusion of other possible causes. In this fashion, the following groups were eventually selected:

1. Cases (158) in which, without consideration of the spinal fluid, a diagnosis of multiple sclerosis was reasonably certain.

2. Cases (45) in which, without consideration of the spinal fluid, a diagnosis of multiple sclerosis was quite possible.

3. Cases (94) in which the diagnosis was definitely not multiple sclerosis but in which the spinal fluid gave a type D colloidal gold reaction.

In addition, all "nonsyphilitic" cases in which there was a type D reaction were analyzed as to probable diagnosis. Of 263 such cases, 169 were "definite" or "probable" cases of multiple sclerosis and 94 fell into group C, noted above.

RESULTS

The results of these investigations are summarized in table 1 and charts 2 and 3. Strong, weak or minimal type D reactions occurred in 94 per cent of our cases with a "definite diagnosis" of multiple sclerosis and in 83 per cent of cases in which the diagnosis of multiple sclerosis either was definite or reasonably suspected (chart 2). This indicates that some form of the type D reaction is to be expected in multiple sclerosis and, on the other hand, that the presence of another type (A, B or C) renders the diagnosis less certain.[10] Continued observations at the Montefiore Hospital have confirmed these results. That our figure of 83 per cent correlates so closely with Kabat's relative increase of gamma globulin in 85 per cent of his cases suggests that they are both manifestations of the same process.

However, the presence of multiple sclerosis in only 64 per cent of all nonsyphilitic patients with type D curves confirms the known fact that the test is not specific for this disease but that the type D reaction may occur in a variety of disorders of the central nervous system (chart 3).

10. With respect to those few cases of multiple sclerosis in which type D reactions were not present, it should be noted that in the various phases of such a remissively progressive disorder an invariably characteristic reaction is not to be expected.

Lange holds the view that parenchymal degeneration is the common pathologic factor in cases with which the type D curve is associated.[4b] Type D curves occurred in 36 per cent of the cases in which a diagnosis

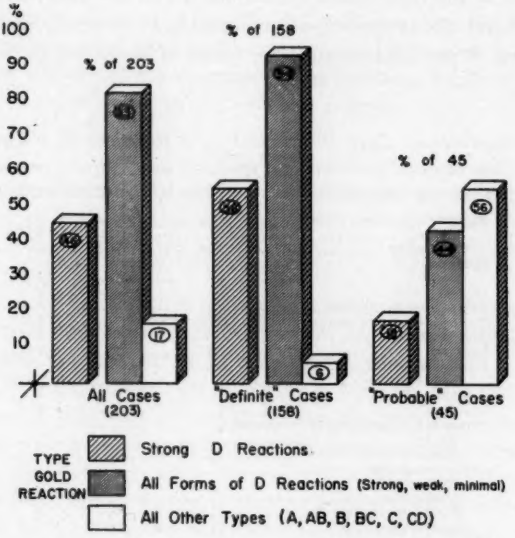

Chart 2.—Types of the D colloidal gold reaction in 203 cases of multiple sclerosis.

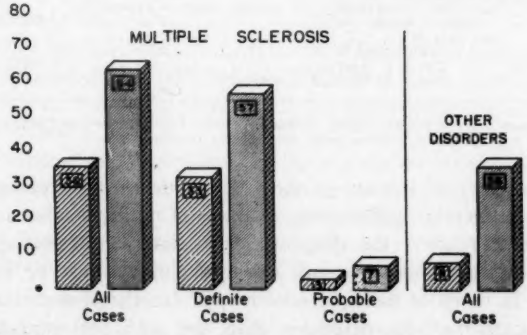

Chart 3.—Types of the D colloidal gold reaction in 263 cases of nonsyphilitic neuropathy. The strong D reactions are indicated by coarse cross hatching; all other forms of the D reaction, by fine cross hatching.

of multiple sclerosis was not likely, even though the reported diagnoses were often not reliable, owing to lack of information. These various disorders are listed in table 2.

When one considers only the stronger type D curves, exclusive of the weak and minimal curves, it is at once apparent that in multiple sclerosis the strong type D reaction occurs much less frequently (46 per cent) than do all of the type D curves combined (83 per cent; chart 2). On the other hand, the strong type D reaction is more nearly specific, occurring in only 8 per cent of all other cases of nonsyphilitic neuropathies (chart 3).

TABLE 2.—*Incidence of Type D Colloidal Gold Reactions in Various Diseases* Other Than Multiple Sclerosis or Syphilis of the Central Nervous System*

Ruptured nucleus pulposis	15	
Proved		9 (2)†
Suspected		6
Brain tumor	8	
Proved		4 (3)
Suspected		4
Brain abscess, proved		1
Tuberculous meningitis, proved, under treatment		5 (4)
Encephalitis		3 (2)
Neuritis		2 (1)
Encephalopathy	6	
Hypertensive		2 (1)
Alcoholic		2
Lead		2
Progressive degenerative diseases	2	
Marie's		1
Charcot-Marie-Tooth		1
Cerebrovascular	17	
Thrombosis		10 (2)
Hematoma		4 (1)
Subdural hematoma		2
Aneurysm		1
Psychoses	22	
Arteriosclerotic		8 (1)
Chronic alcoholic		5
Schizophrenic		6 (1 postencephalitic)
Miscellaneous		3
Idiopathic epilepsy		4
Secondary involvement of central nervous system by diabetes, lupus, etc.		6 (2)
Age over 65		3
Total cases		203
Total D reactions		94 (30%)
Weak or minimal D reactions		79%

* These cases represent unconfirmed diagnoses except when marked as "proved."
† Figures in parentheses indicate cases with strong D curves.

The presence of any one of the type D curves of differing strengths is, therefore, merely confirmatory evidence of multiple sclerosis, whereas their absence renders the diagnosis less certain. A strong reaction, representing only about one-half the total number of type D reactions occurring in cases of multiple sclerosis, is (in the absence of syphilis) more indicative of the diagnosis than are weak or minimal type D reactions.

In cases of multiple sclerosis, both definite and suspected, the total protein concentration of the cerebrospinal fluid specimens ranged from 16 to 139 mg. per 100 cc., with an average of 42 mg. per 100 cc. In 36 per cent the concentration was more than 45 mg. per 100 cc., but in only one was it more than 100 mg. per 100 cc. The cerebrospinal fluid cell

counts ranged from 0 to 39 monocytes, with an average of 3 monocytes, per cubic millimeter. Only 8 per cent of cases showed an elevation above 10 cells per cubic millimeter. In only 5 cases was there any segmented granulocyte reaction.

An attempt to correlate the colloidal gold reaction, the cell count and the protein concentration of the cerebrospinal fluid with the duration and apparent activity of the disorder has as yet been fruitless. Further investigation on this aspect of the problem is under way.

CONCLUSIONS

The quantitative colloidal gold test as performed at, and reported by, the Division of Laboratories and Research of the New York State Department of Health is a valuable aid in the diagnosis of multiple sclerosis.

Multiple sclerosis was the presumptive diagnosis in 64 per cent of the 263 cases of nonsyphilitic disorders in which the spinal fluid showed a type D colloidal gold reaction of one or another strength. Some form of the type D reaction was also found in 36 per cent of a miscellaneous series of cases of disorders of the central nervous system. These findings are in accord with the known lack of specificity of the type D reactions for this or any other disease.

On the other hand, the type D reactions were present in 94 per cent of 158 cases with a "definite diagnosis" of multiple sclerosis and in 83 per cent of 203 cases in which this disorder was either definitely diagnosed or reasonably suspected. Therefore, the absence of the type D reaction (i. e., the presence of any other type of curve) renders a diagnosis of multiple sclerosis uncertain.

The strong type D reaction (exclusive of weak and minimal types) was found less commonly (46 per cent) but was more indicative of the disease, as it occurred rarely (8 per cent) in nonsyphilitic patients without multiple sclerosis.

The presence of the type D colloidal gold reaction in cases of multiple sclerosis and syphilis of the central nervous system closely parallels the relative increase in gamma globulins over albumin in the cerebrospinal fluid, as reported by other observers.

The total proteins were moderately increased in 36 per cent of our cases of multiple sclerosis.

The cerebrospinal fluid cell count was increased to above 10 cells per cubic millimeter in only 8 per cent of the cases of multiple sclerosis.

No correlation was found between the duration, stage or clinical activity of the disorder and the colloidal gold reaction, total protein concentration or cell count of the cerebrospinal fluid.

DEMYELINATING ENCEPHALOMYELITIS FOLLOWING USE OF ANTITETANUS SERUM

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THE ETIOLOGY of the parainfectious and postvaccinal encephalomyelitides still represents an unsettled problem. The theory that the virus of the primary infectious disease itself causes the demyelinating encephalomyelitis has been fairly generally abandoned during the last decade. The same statement can be made concerning the activation theory, which claims that an agent different from the virus of the basic disease, and living in the organism in a latent state, is activated. However, the possible etiologic role of a living agent has recently been supported by Margulis, Soloviev and Shubladze,[1] who recovered a neurotropic virus from the blood in one case and of encephalomyelitis from the brain tissue in another.

Most investigators nowadays favor the allergy theory, advanced in 1927 by Glanzmann for the explanation of vaccinal encephalitis and developed by Pette[2] on the basis of clinical and histopathological investigation of the human diseases for the whole field of the leukoencephalomyelitides, including multiple sclerosis. The allergy theory gained a broad experimental basis from the studies of Rivers,[3] Ferraro,[4]

From the Pathologic Laboratory of the Municipal Hospital; Director, S. Wiltner, M.D.

1. Margulis, M. S.; Soloviev, V. D., and Shubladze, A. K.: Aetiology and Pathology of Acute Sporadic Disseminated Encephalomyelitis and Multiple Sclerosis, J. Neurol., Neurosurg. & Psychiat. **9**:63, 1946.

2. (*a*) Pette, H.: Die akut entzündlichen Erkrankungen des Nervensystems, Leipzig, Georg Thieme, 1942; (*b*) Das Problem der Entmarkungsencephalomyelitiden in dynamischer Betrachtung, Klin. Wchnschr. **24-25**:897, 1947.

3. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689, 1935.

4. (*a*) Ferraro, A.: Allergic Brain Changes in Post-Scarlatinal Encephalitis, J. Neuropath. & Exper. Neurol. **3**:239, 1944. (*b*) Ferraro, A., and Cazzullo, C. L.: Chronic Experimental Allergic Encephalomyelitis in Monkeys, ibid. **7**:235, 1948. (*c*) Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

Morrison [5] and others, who succeeded in producing a demyelinating inflammatory process in the central nervous system of the monkey, rabbit and guinea pig.

Demyelinating encephalomyelitis has been observed as a sequela of the infectious diseases measles, smallpox, chickenpox, influenza, epidemic parotitis, scarlet fever and, recently, Q fever (Wegmann [6]) and of vaccinations against smallpox, rabies, pertussis and typhoid. Histological examinations showed an identity of the neural process independent of the nature of the basic disease or the vaccine used. This point was emphasized by Környey.[7] Neurological complications after prophylactic or therapeutic applications of serums have been, even clinically, much less frequently observed, and in cases of such complications lesions of the peripheral nerves have been recorded far oftener than lesions of the central nervous system. Nevertheless, the scattered observations led Pette [2a] to the opinion that administration of protecting serums may play a prominent part in the pathogenesis of demyelinating encephalomyelitis.

The following case seems to be the first verified instance of leukoencephalomyelitis following the administration of tetanus antitoxin and hence is worthy of being recorded.

REPORT OF A CASE

History.—N. M., a highroad worker aged 35, was admitted to the medical service (Dr. Böhm) of the Municipal Hospital on Dec. 4, 1948. His family history was without significance. He had measles as a small child and typhoid at the age of 20. He was said never to have been given horse serum. He had been vaccinated against smallpox in childhood and against typhoid in 1945.

Ten days before admission he sustained a small wound on his left hand while at work. He received 2,500 international units of tetanus antitoxin intramuscularly. On the third day thereafter generalized urticaria developed, followed by malaise, headache, low back pain and general weakness. The wheals disappeared in six days, but his skin remained hyperesthetic, the slightest touch eliciting almost unbearable pain, as though it were "being torn." On the tenth day after the injection of serum, his condition suddenly became worse; the right extremities became paralyzed; the headache increased, and he lost consciousness within a few hours.

Examination.—On examination, the patient uttered only unintelligible syllables. On the day of admission he had no fever, but on the next day a temperature of 40 C. (104 F.) was recorded. The chest and abdomen presented a normal

5. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by the Use of Homologous Antigen, Arch. Neurol. & Psychiat. **58**:391 (Oct.) 1947.

6. Wegmann, T.: Encephalitis nach "Q fever," Schweiz. med. Wchnschr. **79**:690, 1949.

7. Környey, S.: Akute nichtspezifische, nichteitrige entzündliche Erkrankungen des Gehirns und Rückenmarks beim Menschen, Ergebn. d. allg. Path. u. path. Anat. **36**:96, 1943.

condition. The urine was normal. The blood pressure was 130 mm. of mercury systolic and 100 mm. diastolic. The leukocyte count was 7,400.

Neurological examination showed that the right pupil was of medium size, round and responsive to light; the left pupil could not be examined because of a corneal scar. The radial reflex was absent on both sides. The knee jerk was absent on the left side and the ankle jerk on both sides. There were spastic paresis of the right side and retention of urine.

Lumbar puncture revealed a clear, but slightly yellowish, cerebrospinal fluid, which was under high pressure. The Pándy reaction was negative, and the cell count was 540 per 3 cu. mm. The majority of the cells were lymphocytes, but a small number of segmented granulocytes and erythrocytes were also seen. The Wassermann reactions, both of the blood and of the cerebrospinal fluid, were negative.

Fig. 1.—Distribution of the hemorrhages and dilated vessels in a coronal section of the left parieto-occipital region and posterior part of the thalamus.

The patient died on the fourteenth day after the administration of serum.

Necropsy.—Necropsy, 10 hours after death, revealed no pathological changes in the internal organs, other than the nervous system, except for a small, early focus of bronchopneumonia in the lower lobe of the right lung.

Brain: Palpation of the left parietal lobe revealed an area about the size of a nut which appeared softer than the rest. No other gross change was visible or palpable on the surface of the brain. Cross sections made after fixation in dilute solution of formaldehyde U.S.P. for six days revealed numerous soft yellowish foci, the size of a bean to that of a hazelnut, enclosing a large number of densely occurring hemorrhagic spots (fig. 1). This yellowish color disappeared during the latter part of the fixation. The localization of the foci was fairly symmetric. In the frontal and temporal lobes no macroscopic changes were recognizable except for hyperemia, but an increasing number of foci appeared in the more caudal levels, so that in the parieto-occipital region

the subcortical white matter of nearly all convolutions, especially over the convexity, presented this change. Only the occipital pole remained free of it. A small number of foci were observed in the corpus callosum. No foci were visible in the cortex or in the basal ganglia, although the latter were excessively hyperemic. Similarly, hyperemia was the only macroscopic change present in the cerebellum, pons and medulla oblongata.

A few widely scattered hemorrhagic spots were present in the white substance of the spinal cord, which otherwise showed diffuse hyperemia.

The leptomeninges of the brain and spinal cord were hyperemic.

Histological Study: Sections from many regions of the brain and spinal cord were stained and impregnated by various methods. The most characteristic and conspicuous change was perivascular demyelination. The slightest degree of the process was represented by a thin cuff of inflammatory and scavenger

Fig. 2.—Confluent perivascular demyelinated foci in the subcortical layer of a parietal convolution. Frozen section; Spielmeyer stain for myelin sheaths.

cells around a small vessel. In the foci of severer alteration a central vessel was surrounded by a bright ring, without myelin and almost acellular; around this was a circular myelinophagic zone with scavenger cells (fig. 3). The content of the scavenger cells had an affinity both for myelin and for fat stains. Foci were present in nearly all parts of the brain. In the cerebellum they were few. The cervical and thoracic portions of the cord were severely affected. The corpus callosum, the pons, the medulla and the lumbar portion of the cord formed an exception, there being no change in these regions except for hyperemia. The demyelinated areas were restricted to the white matter, and there chiefly to the subcortical layers (fig. 2). Perivascular foci were located in the neighborhood of the occipital horn on each side, but the periventricular regions were not especially preferred by the process. The perivascular demyelinated areas were fairly sharply delimited, although in their vicinity rosary-like, thickened or irregularly swollen myelinated fibers and scattered scavenger cells might be visible.

In some places several neighboring vessels or several branches of the same vascular trunk were surrounded by demyelinated foci. This led to a more or less conspicuous confluence of the foci (fig. 2). Obviously, the corresponding areas were recognizable as yellowish territories on macroscopic examination.

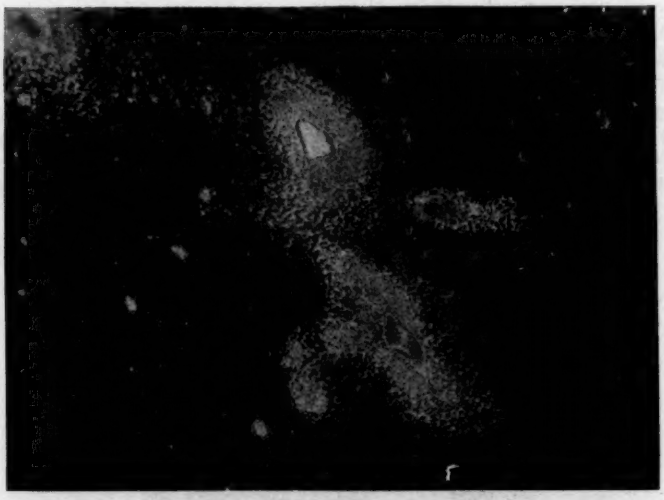

Fig. 3.—Higher magnification of a portion of the field shown in figure 2.

Fig. 4.—At the left, exudation of plasma around, and endothelial swelling in, the wall of a precapillary vessel. At the right, slight adventitial infiltration of a small artery. Hematoxylin-eosin stain.

The lesions of the axis-cylinders as seen in the Bielschowsky preparations were less severe than those of the myelin sheaths. Only in the highly damaged areas were the axis-cylinders also fragmented.

In toluidine, hematoxylin-eosin and hematoxylin-Van Gieson preparations it could be ascertained that the inner zone of the perivascular area consisted of extravasated plasma (fig. 4), in which scattered scavenger cells and hematogenous elements were embedded. As is usual in the parainfectious and postvaccinal encephalomyelitides, the foci were localized around the small veins and capillaries (figs. 3 and 4). The smaller the vessel, the more likely was the extravasation of plasma to be present. Cellular infiltration around the smaller vessels was practically absent, whereas the wall of some small arteries and veins was infiltrated with lymphocytes, with which scattered segmented granulocytes and plasmacytes were mingled.

Considerable structural change was seen in the wall of the vessels, especially in the intima, which was generally swollen.

No thrombus formation was observed. This fact constituted a contrast to Putnam's observation and his assumption that the destruction of myelin sheaths is due to thrombus formation.

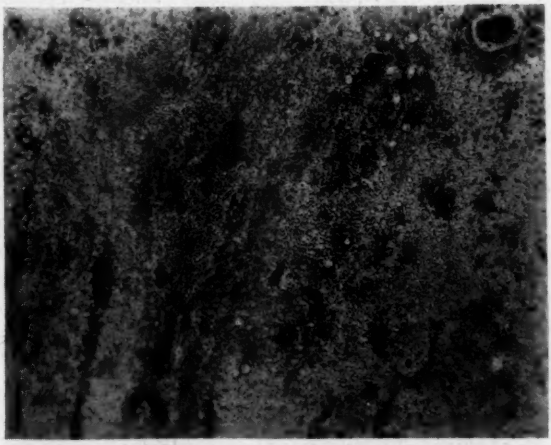

Fig. 5.—Perivascular infiltration, exudation of plasma and necrosis in the white matter of the cervical portion of the spinal cord. Toluidine stain.

Erythrocytes were not extravasated as often as was to be expected on the basis of the gross examination. The macroscopically red spots represented mainly hyperemic vessels, and seldom hemorrhages.

Generally the histological changes in the spinal cord were identical with, but less severe than, those in the brain (fig. 5). Demyelination was present in the posterior, and still more in the lateral, funiculi.

In the leptomeninges only hyperemia, without extravasation of plasma or blood cells, could be detected.

COMMENT

The intramuscular injection of 10 cc. of horse serum containing 2,500 international units of tetanus antitoxin was followed by urticaria on the third day and by signs of a cerebrospinal lesion, which became definite on the tenth day. The patient died on the fourteenth day after

the administration of serum. The histologic picture corresponded to that of a parainfectious or postvaccinal leukoencephalitis. Slight inflammation and marked demyelination were accompanied with extensive effusion of plasma. The central position of vessels in the demyelinated foci was so characteristic as to give the impression that the damaging substance had diffused from the lumen and dissolved the surrounding parenchyma, i. e., the myelin sheaths. The exclusively perivascular arrangement of the plasma effusion and the other changes remind one of the view of Rössle,[8] Klinge,[9] Gerlach and others, according to which extravasation of plasma is one of the most typical signs of hyperemic inflammation.

Small perivascular areas of demyelination and glial proliferation have been mentioned in the histopathology of tetanus for more than half a century. Ancient descriptions cannot be evaluated because of the inadequate technic of such studies. In the recent literature, Baker[10] reported several cases in which similar foci were noted. Even when they occur in cases in which serum was not given they seem not to be numerous enough to be comparable to the extensive process in the present case.

Thus, the histological analysis of this case justifies the assumption that the process represents a neuroallergic reaction. From this point of view, it may seem strange that few eosinophilic cells were found. Their massive occurrence would be an argument in favor of an allergic origin. However, infiltrations of eosinophils are known mainly in arsphenamine encephalopathy, whereas in cases of both human and experimental leukoencephalomyelitis their presence seems not to be the rule, or even an exception.

As to the cause and pathological mechanism of the allergic reaction, the past history in the present case offers no explanation. The patient was said never before to have received horse serum, and nothing supports the assumption of an aspecific sensitization. Cases of encephalomyelitis following administration of serum or vaccination with histological studies have been reported except for the well known cases following smallpox and rabies vaccination. Giffin, Rogers and Kernohan[11] published recently the results of histological examination in a

8. Rössle, R.: Zum Formenkreis der rheumatischen Gewebsveränderungen, mit besonderer Berücksichtigung der rheumatischen Gefässentzündungen, Virchows Arch. f. path. Anat. **288**:780, 1933.

9. Klinge, F.: Der Rheumatismus: Pathologische-anatomische und experimentell-pathologische Tatsachen und ihre Auswertung für das ärztliche Rheumaproblem, Ergebn. d. allg. Path. u. path. Anat. **27**:1, 1933.

10. Baker, A. B.: The Central Nervous System in Tetanus, J. Neuropath. & Exper. Neurol. **1**:394, 1942.

11. Giffin, M. E.; Rogers, H. M., and Kernohan, I. W.: Postvaccinal (Typhoid) Encephalitis, Arch. Neurol. & Psychiat. **59**:233 (Feb.) 1948.

case of encephalitis following vaccination against typhoid. The histological changes corresponded entirely to those we observed in our case.

With respect to the neurological complications of administration of tetanus antitoxin, Putnam [12] produced perivascular demyelination experimentally in dogs by repeated injections of tetanus antitoxin. Clinical reports on complications in man were made by Kroll,[13] Schipkowensky [14] and Strotzka and Waldschütz.[15] A case of meningitis with histological examination was reported by Spaar [16] and the condition interpreted as of allergic origin. In this case necropsy revealed a fulminant meningitis with perivascular exudation, erythrocytic and leukocytic infiltration and fibrinoid swelling of the vessel walls. Small perivascular demyelinated foci were also noted in the corpora quadrigemina and in the corpus callosum. However, the inflammatory reaction was limited to the meninges.

An increasing number of neural complications of vaccination and serum treatment have been reported during recent years. This is undoubtedly due to the extension of these preventive and therapeutic methods. It may be mentioned that 15 cases of encephalomyelitis were observed in England after pertussis vaccination in 1948.[17] The manifestation of multiple sclerosis after the Mantoux test was reported recently by Mérei.[18]

The concept that the antigen reaches the brain substance through the vessels is becoming adopted. The histological changes support this concept, because, as in the present case, the escape of plasma bears a definite relation to the destruction of myelin. Extensive demyelination in this case was found only where extensive effusion of plasma was present. Furthermore, a comparison of serial sections stained with different methods showed about the same extension of demyelination and extravasation of plasma. If in the smallest perivascular demyeli-

12. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

13. Kroll, F. W.: Tetanusserum-Myelitis nach 2 maliger Serumimpfung, Nervenarzt, **11**:252, 1938.

14. Schipkowensky, N.: Schädigungen des Nervensystems bei Serumkrankheit (Beobachtung an drei neuen Fällen), Arch. f. Psychiat. **106**:779, 1937.

15. Strotzka, H., and Waldschütz, J.: Zur Kenntnis allergischer Erkrankungen des Zentralnervensystems, Klin. Med. **10**:371, 1949.

16. Spaar, R.: Allergische Meningitis bei Tetanus, Arch. f. Psychiat. **116**:1, 1943.

17. Encephalopathy Following Pertussis Vaccine, Annotation, Lancet **1**:699 (April 23) 1949.

18. Mérei, F.: Neurologic Complications Following Mantoux Test, Arch. Neurol. & Psychiat. **63**:249 (Feb.) 1950.

nated areas no effusion of plasma can be demonstrated, this is probably because the present histological technics are not suited to render visible slight degrees of plasma effusion.

The assumption seems justified that antibodies (reagins) in the nervous system are produced exclusively by adventitial histiocytes and mesoglial cells. The circulating antigen comes into contact with the antibodies by transvascular diffusion. Effusion of plasma cannot take place unless the walls of the vessels are damaged. It is probable that the antigen-antibody reaction produces a new substance which destroys the myelin sheaths.

SUMMARY

The case is reported of a man aged 35 who had a generalized urticaria on the third day after injection of 1,500 international units of tetanus antitoxin, followed by symptoms and signs of a cerebrospinal process. Death occurred on the fourteenth day after administration of serum. Histologically, perivascular effusions of plasma and demyelination were observed. Significance is to be attributed to the case with respect to the pathogenesis of demyelinating encephalitis, for the following reasons:

1. The histological process was identical with that present in cases of parainfectious or postvaccinal encephalomyelitis.

2. The clinical pattern and histological changes prove that the process was of allergic nature.

3. Histological studies yield strong support for Pette's theory of neuroallergy and demonstrate the value of the experimental results of Ferraro and others from the standpoint of human medicine.

PRODUCTION OF CONVULSIONS BY ADMINISTRATION OF BENZEDRINE® FOLLOWING BRAIN OPERATIONS IN MONKEYS

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AND
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CONVINCING evidence has been presented [1] that areas of pathological function in the brain may cause more deleterious effects than clear removals of the tissue concerned. In the clinical field, it is becoming accepted that cases of scar, atrophy, abscess, neoplasm, etc., are poorly suited to purposes of localization of function. What is not so well recognized is that experimental ablations are likewise not exempt from surgically produced artefact. Scarring, vascular anomalies and residual necrotic tissue may result in foci of irritation which produce effects remote from the site of injury. Although these foci may not be epileptogenic in themselves, the fact that the introduction of sensitizing agents may cause them to become so [2] suggests that they are potential sources of subtler disruptions of cerebral function. Such factors may account for many of the contradictions and discrepancies in the experimental literature.

A possible indication of the existence of irritative effects after cerebral lesion is the fact that brain damage reduces seizure thresholds, as previous studies [3] have shown. These studies have employed various

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From the Yerkes Laboratories of Primate Biology and Yale University.

1. Hebb, D. O.: Organization of Behavior: A Neuropsychological Theory, New York, John Wiley & Sons, Inc., 1949, pp. 271-274.

2. Kopeloff, N.; Kopeloff, L. M., and Pacella, B. L.: The Experimental Production of Epilepsy in Animals, in Hoch, P. H., and Knight, R. P.: Epilepsy: Psychiatric Aspects of Convulsive Disorders, Proceedings of the Thirty-Sixth Annual Meeting of the American Psychopathological Association, New York, Grune & Stratton, Inc., 1947, pp. 164-180.

3. Muncie, W. S., and Schneider, A. J.: A Study of the Convulsions Produced by Wormwood, Bull. Johns Hopkins Hosp. **42**:77-92, 1928. Steelman, H. F.: Technic of Cortical Excision: An Experimental Study of Postoperative Cicatrization, Arch. Neurol. & Psychiat. **62**:479-492 (Oct.) 1949. Ransohoff, J., and Carter, S.: Experimental Studies in Post-Traumatic Epilepsy: Preliminary Report, J. Neuropath. & Exper. Neurol. **8**:446-449, 1949.

surgical technics and a number of different convulsant agents. The present investigation is concerned with the incidence of amphetamine (benzedrine®)-induced convulsions after lesions made by subpial suction, which is now considered the surgical method of choice. The effects on locomotor activity are also of interest in connection with Ruch's [4] finding that hyperactivity in prefrontal preparations is eliminated by the administration of amphetamine.

METHODS

Twenty-eight monkeys (25 Macaca mulatta and three Ateles geoffroyi) were the subjects of this experiment. Twenty of these animals had had bilateral cortical ablations at intervals varying from two months to two years before administration of the drug. They had been used in behavioral studies and had been trained on a variety of problems. The eight untrained monkeys without brain operations were used as controls.

All the extirpations were performed by aspiration, using aseptic technic. None of the animals had any spontaneous convulsions before or after operation. Recoveries were uneventful.

Eight monkeys had ablations anterior to the central fissure (six with subtotal prefrontal and two with premotor lesions). Nine monkeys had lesions in the posterior parts of the cortex (one, postcentral and posterior parietal; two, posterior parietal; two, temporo-occipital; two, prestriate, and two, temporal lesions). Three animals had combined lesions of the prefrontal and parietotemporal regions.

Amphetamine sulfate was given subcutaneously in doses ranging from 1.4 to 18.0 mg. per kilogram of body weight. Some of the animals were used only once; others had progressively larger doses on successive occasions, separated by at least one day. The animals were under constant observation for at least 12 hours after injection of the drug. They were confined in small cages, 16 by 22 by 28 inches (40 by 55 by 70 cm.) and kept in a building remote from their living quarters during the period of observation. Protocols were kept on their general behavior, with particular reference to incidence of convulsions, level of activity and motor symptoms (tremors; stereotyped, repetitive movements; ataxia, etc.). Most of the animals who had seizures were killed immediately thereafter.

RESULTS

Incidence of Convulsions (table 1).—Convulsions occurred in 50 per cent of the animals with cortical ablations, but in none of the normal monkeys. For these data, the value of chi-square (1 degree of freedom), with the Yates correction for small numbers, was 4.4, which is significant between the 5 and 2 per cent levels of confidence.

The convulsions were of two types. The generalized seizures started with an intense tonic contraction, followed by clonus of all four limbs. The seizures we have called jacksonian began with localized clonic contractions (in the face, in one limb, in both arms or in the arm and leg of the same side) and spread progressively to the rest of the body.

4. Ruch, T. C.: Association Areas and the Cerebral Cortex in General, in Howell, W. H.: Howell's Textbook of Physiology, ed. 15, Philadelphia, W. B. Saunders Company, 1946, p. 536.

Seizures usually lasted about 20 seconds and occurred repetitively with successively shorter intervals of flaccidity (from a few minutes to a few seconds).

Biserial correlations were computed between the number of months since operation and the occurrence of convulsions, and between weights and convulsions. Both these correlations were near zero.

TABLE 1.—*Incidence of Convulsions in Monkeys with Brain Operations and in Normal Monkeys After Administration of Amphetamine*

No.	Operative Site	Months After Operation	Weight (Kg.)	Dosage (Mg./Kg.)	Convulsions
1*	Prefrontal	14	3.6	2.8	Jacksonian
2	Prefrontal	26	4.8	4.2, 6.6, 8.4	None
3	Prefrontal	26	5.0	4.0, 6.0, 8.0	None
4	Prefrontal	15	4.8	4.2	Generalized
5	Prefrontal	24	4.3	1.4, 4.6†	Jacksonian
6	Prefrontal	18	4.0	3.0, 5.0, 7.5	Generalized
7	Premotor	4	2.7	7.5, 11.1	Jacksonian
8	Premotor	4	2.7	7.5, 11.1	Jacksonian
9	Postcentral parietal	5	2.1	4.8	Jacksonian
10	Parietal	3	2.7	7.5, 11.1	None
11	Parietal	2	2.0	18.0	Generalized
12	Temporo-occipital	2	2.0	18.0	Jacksonian
13	Temporo-occipital	3	2.3	4.3, 10.8	None
14	Prestriate	2	2.5	15.0	None
15	Prestriate	3	2.3	16.0, 17.4	None
16	Temporal	7	3.0	1.7, 3.3, 3.3, 12.0	None
17	Temporal	4	2.7	7.5, 11.1	None
18	Prefrontal, parietotemporal	3	2.7	3.7, 7.5, 8.9, 11.1	None
19	Prefrontal, parietotemporal	10	4.3	4.7, 6.9, 6.9, 9.3	None
20	Prefrontal, parietotemporal	9	5.0	4.0, 6.0	Generalized
21‡	Normal	..	6.4	6.2	None
22‡	Normal	..	6.0	3.3	None
23‡	Normal	..	7.0	18.0	None
24	Normal	..	3.0	3.3, 13.3	None
25	Normal	..	2.3	8.7	None
26	Normal	..	2.7	7.5, 11.1	None
27	Normal	..	2.4	4.2	None
28	Normal	..	2.4	3.0, 9.2, 18.0	None

* A preliminary report of the occurrence of seizures in this animal appeared in Science **108**: 560-561, 1948.

† In the cases in which different amounts of the drug were given on several occasions, the indicated convulsions occurred after only the highest doses recorded.

‡ These subjects were At. geoffroyi; the rest were M. mulatta.

Individual variation in susceptibility to the effects of the drug obscures the relationship of dosage to occurrence of seizures. Convulsions occurred in some of the surgical group with doses of 2.8 to 18.0 mg. per kilogram. In other animals of this group no convulsions occurred with doses of 1.4 to 17.4 mg. per kilogram; the normal group failed to have seizures with doses of 3.0 to 18.0 mg. per kilogram. The average dose producing convulsions was 8.8 mg. per kilogram. Of the

18 monkeys who did not have convulsions, 12 received doses larger than this value. The absolute amount of the drug employed per unit of body weight appears to be less significant than other variable influencing convulsive propensity.

The incidence of convulsions was considered in relation to location and mass of cortical damage. All three monkeys with lesions bordering on the precentral gyrus (one with postcentral and parietal ablation and two with premotor removals) had convulsions. Of six monkeys with lesions anterior to the premotor region, four convulsed. Of eight monkeys with lesions caudal to the postcentral gyrus, two convulsed. One of the three animals with combined posterior and frontal lesions had

TABLE 2.—*Number of Monkeys with Brain Operations and of Normal Monkeys in Which Alteration of the Level of Gross Activity Was Produced by Administration of Amphetamine*

	Total Number of Subjects	Activity				
		Marked Decrease	Slight Decrease	No Change	Slight Increase	Marked Increase
Experimental animal						
Prefrontal	6	2	1	..	..	3
Premotor	2	..	..	..	1	1
Postcentral and parietal	1	..	..	..	..	1
Parietal	2	..	..	1	1	..
Temporal	2	..	..	1	..	1
Temporo-occipital	2	..	..	2	..	..
Prestriate	2	1	..	1	..	..
Prefrontal and parietotemporal	3	2	..	1	..	..
Controls	8	1	..	5	1	1

seizures. The differences in frequency of convulsions in these four groups is not significant by the contingency test.

Although precise estimates of the mass of the lesion have not been made, it is noteworthy that only one of the three animals with the largest lesions (combined destruction of the entire lateral surface of the parietal and temporal lobes, and of the prefrontal region) convulsed. The next largest lesion was the postcentral and parietal removal (parietal lobectomy) in animal 9, which had convulsions. The other lesions were relatively small, subtotal removals of the frontal, parietal or temporal lobes; of 16 animals with such lesions, eight had seizures.

Activity (table 2).—All the nine monkeys with prefrontal lesions were hyperactive prior to administration of the drug. Injection of amphetamine produced a marked decrease of locomotor activity in four animals (dose, 3.0 to 8.4 mg. per kilogram), a slight increase in one (dose 4.0 to 8.0 mg. per kilogram), marked increase in three (dose, 2.8 to 4.6 mg. per kilogram) and no change in one (dose, 3.7 to 11.1 mg. per kilogram). These effects were consistent for the individual

monkey on different days, when the drug was administered in varying doses. Forced movements (such as head turning, chewing and biting the cage wires), tremors and tics appeared to a striking extent in those animals which showed decrease of locomotor activity, whereas this was not the case in the animals whose locomotor activity increased.

None of the other 19 subjects was hyperactive. Administration of amphetamine produced no change in level of activity in 10 of them (dose, 1.7 to 18.0 mg. per kilogram), marked decrease in two (dose, 8.7 to 17.4 mg. per kilogram), slight increase in three (dose, 7.5 to 11.1 mg. per kilogram) and marked increase in four (dose, 1.7 to 12.0 mg. per kilogram). This increase should not be confused with the stereotyped pacing seen after prefrontal removal. It consisted, rather, of irregular darts, runs and jumps. In this group, there was apparently no correlation between level of gross locomotor activity and forced or clonic movements.

Mortality.—Six monkeys of the group with cortical removals (monkeys 4, 5, 9, 11, 12 and 20) died after having convulsions. One of the surgical group (monkey 14) and four control animals (monkeys 24, 25, 26 and 27) died in coma without prior convulsions. The minimum lethal dose, of those given in this study, was 4.2 mg. per kilogram. This figure approximates that given by Ehrich, Lewy and Krumbhaar [5] for young macaques.

COMMENT

Our results support and extend the conclusions of previous investigations that susceptibility to induced seizures is increased by brain damage. Although the lesions in our subjects were made by scar-minimizing technic, i. e., subpial suction, convulsions occurred in half the surgical group after administration of amphetamine. Steelman found that the minimal dose of metrazol® producing convulsions in a group of macaques operated on in this manner was reduced an average of 40 per cent from preoperative values. Both these findings indicate that even the most favored surgical procedure produces potentially irritative effects.

The lack of relation between incidence of convulsions and various other factors considered in this study is somewhat unexpected. Jasper, Kershman and Elvidge [6] have shown that focal or generalized abnormalities of the electroencephalogram may follow cortical injury and cited evidence that, although these irregular slow potentials may persist for years, they tend to disappear in the course of time. The period between

5. Ehrich, W. E.; Lewy, F. H., and Krumbhaar, E. B.: Experimental Studies upon the Toxicity of Benzedrine Sulphate in Various Animals, Am. J. M. Sc. **198**:785-803, 1939.

6. Jasper, H.; Kershman, J., and Elvidge, A. E.: Electroencephalography in Head Injury, A. Research Nerv. & Ment. Dis., Proc. (1943) **24**:388-420, 1945.

operation and administration of the drug to our subjects varied from two months to more than two years; yet we found no correlation between length of time after operation and incidence of seizures. The lack of correlation with weight is also of interest, as it might have been hypothesized that age, and hence weight, would be related to convulsant effect. Similarly, our data do not lend support to the possibility that increased susceptibility to the excitatory effects of stimulants of the central nervous system is related to extent of damage to cortical tissue (which might be assumed to have an inhibitory function). The mass of cortical tissue removed appears to be an insignificant factor in this connection. The effectiveness of the small lesions made by Muncie and Schneider in reducing seizure thresholds likewise suggests the relative unimportance of the amount of cerebral destruction.

One of the principal interests of this study was to determine whether disorders of behavior following brain lesions are correlated with occurrence of amphetamine-induced seizures. In an earlier publication,[7] we assumed that convulsions after administration of amphetamine were significant of the presence of a focus of irritation, which might also be productive of observed behavioral abnormalities. All our subjects with cortical removals were used in studies which necessitated extensive preoperative and postoperative tests and observations. The tests used included visual, auditory and somatosensory discrimination problems and delayed reaction. In none of these tests was postoperative performance correlated with seizures. Seven of the 20 animals with cortical removals both had seizures and showed deficits; three neither had seizures nor showed deficits, and 10 either had seizures but no deficits or had deficits but no seizures. The level of general activity was also measured and was apparently unrelated to the convulsant effect of amphetamine. The postulation that postoperative alterations of behavior are related to irritative processes which become supraliminal for fits after amphetamine sensitization thus fails to find confirmation in these data. Either the hypothesis that behavioral disturbances are ascribable to pathological function of residual tissue rather than to loss of parts of the nervous substrate is incorrect, or the epileptogenic irritation which becomes manifest after injection of amphetamine is not the same as that producing impairment in the tested performances.

Our findings with regard to the influence of location of lesion on susceptibility to seizures are inconclusive. The number of cases in each lesion category was small, but the data suggest that lesions rostral to the superior postcentral sulcus render the subjects particularly vulnerable to induced seizures. This possible regional difference in

7. Blum, R. A.; Blum, J. S., and Chow, K. L.: The Production of Unilateral Epileptiform Convulsions from Otherwise Quiescent Foci by the Administration of Benzedrine, Science **108**:560-561, 1948.

epileptogenesis should be checked in further experiments. The presence of the motor cortex in this region may not be an adequate explanation, for the fit-producing frontal lesions in this study were in no closer proximity than the posterior lesions to the electrostimulable zone.

The effect of amphetamine on hyperactivity of monkeys with prefrontal lesions appears to be variable. The level of activity in only five of the nine animals was decreased, and in three it was actually increased. Activity in our prefrontal preparations was inversely correlated with the occurrence of other stereotyped movements and tremors. In other animals, with smaller doses of amphetamine, we have observed the quieting effect reported by Ruch. Sedation in these cases occurred without the accompaniment of the "substitute" activity noted in the present series of animals. However, the range of doses we employed in this study had consistent effects both on pacing and on other repetitive forms of motility for a given subject on different occasions with different doses. The relation of dosage to motor effect is probably not a simple one and requires further investigation.

SUMMARY

Twenty-eight monkeys (M. mulatta and A. geoffroyi) were given amphetamine sulfate in doses ranging from 1.4 to 18.0 mg. per kilogram. Twenty of these monkeys had had cortical ablations, made by subpial suction, in various regions from 2 to 26 months before administration of the drug; the other eight served as normal controls. Convulsions occurred in 50 per cent of the animals with cortical removals but in none of the controls. The minimal dose producing convulsions was 2.8 mg. per kilogram. The minimal lethal dose was 4.2 mg. per kilogram.

The effect of amphetamine on hyperactivity in prefrontal preparations was variable from animal to animal, but was consistent for the individual subject for various doses.

No relation could be demonstrated between incidence of seizures and mass of lesion, length of time since operation, age (as indicated by weight), consistent level of previous activity or performance of various learned discriminative reactions. The data suggest that location of the lesion is more closely related to occurrence of induced seizures than are the other variables considered.

"FALSE" LOCALIZING SIGNS IN INTRACRANIAL TUMOR

Report of a Patient with Left Trigeminal Palsy Due to Right Temporal Meningioma

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"FALSE" localizing signs in patients with intracranial tumor are those which when interpreted as being caused by direct involvement by tumor lead the focal diagnosis into error, owing to the fact that the signs are due to processes operating at a distance from the tumor. As Nielsen [1] has said, the signs truly indicate failure of function at their respective sites, and the falsity enters with the interpretation. A sign regarded as false by one generation may lose that designation when the mechanism producing the sign becomes known and the correct significance is attached to it.

The line separating true signs from false signs is sometimes indistinct, and it is not always possible to make rigid distinctions between signs relating to the site of the lesion, signs of a neighborhood nature, due to glial reaction or edema about the lesion or other cause, and signs at a distance, due to the same processes or other processes yet to be mentioned.

Several accounts [2] of false localizing signs include the process of glial reaction about a tumor, whereas perhaps most neurosurgeons, accustomed as they are to finding themselves in the neighborhood of a neoplasm and yet unable to delineate it without resort to multiple cannula explorations, might not distinguish as false the signs leading them only slightly astray in the tumor-bearing hemisphere, but might be content to classify them as neighborhood signs.

It is apparent that this subject is rich in possibilities for splitting hairs. As a practical matter, whether a sign is true or false depends on how accurately or how erroneously it indicates to the examiner the site of the principal lesion. The signs cannot be considered alone and

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Read at the annual meeting of the Neurosurgical Society of America, Quebec, Canada, Nov. 2, 1949.

The patient herein described was observed at the clinic of the Scott and White Hospital, Temple, Texas, during my association with that clinic.

1. Nielsen, J. M.: A Textbook of Clinical Neurology, New York, Paul B. Hoeber, Inc., 1941.

2. (*a*) Nielsen.[1] (*b*) Rand, C. W., and Halsey, W. H.: False Localizing Signs of Cerebral Tumor, Bull. Los Angeles Neurol. Soc. **2**:84-88, 1937.

without reference to the patient in whom they occur, the rest of the findings present, the time of their occurrence and the attitude of the examiner toward them.

The existence of a group of signs which could not be accepted at face value in patients with intracranial tumors was recognized prior to Collier's [3] account, in 1904, for Oppenheim [4] stated earlier that tumors are known to act at a distance either to irritate or to paralyze and that focal signs are not of much diagnostic value if signs of general increased intracranial pressure are pronounced. It is, however, the publication by Collier which may be taken as the beginning of studies relating to false signs as such. Collier found such signs to be present in 12.5 per cent of his 161 consecutive cases and noted that they appeared late in the course of the disease. He listed the then current explanations of the signs (vascular lesions, meningitis, hydrocephalus, local spreading edema of the brain, secondary deposits of new growth and posterior degeneration) and added one of his own (traction on cranial nerves, the sixth especially, consequent on backward shift of the brain stem). Since then many additional mechanisms have been described,[5] along with many falsely occurring signs not mentioned in Collier's series, with the result that almost all the common paralytic and irritative abnormalities of the cranial nerves, the visual pathways and the cerebral and cerebellar lobes have been observed, on occasion, in patients not having tumors in sites generally signalized by the various abnormalities.

In the tabulation are listed, with bibliographic references, most of the proposals made in print to explain false signs. No purpose would

3. Collier, J.: The False Localizing Signs of Intracranial Tumor, Brain **27**:490-507, 1904.

4. Oppenheim, H.: Diseases of Nervous System: A Textbook for Students and Practitioners, translated by E. E. Mayer from the second German edition, Philadelphia, J. B. Lippincott Company, 1900.

5. (*a*) Cushing, H.: Strangulation of the Nervi Abducentes by Lateral Branches of the Basilar Artery in Cases of Brain Tumor, with an Explanation of Some Obscure Palsies on the Basis of Arterial Constriction, Brain **33**:204-235, 1910. (*b*) Gould, E. M.: Tumors of the Posterior Cranial Fossa: Homolateral and Contralateral Pyramidal Tract Signs, Arch. Neurol. & Psychiat. **19**:509-514 (March) 1928. (*c*) Grey, E.: Studies on the Localization of Cerebellar Tumors: V. The Cranial Nerves, Johns Hopkins Hosp. Bull. **27**:251-262, 1916. (*d*) Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. **21**:274-287 (Feb.) 1929. (*e*) Meyer, A.: Herniation of the Brain, ibid. **4**:387-400 (Oct.) 1920. (*f*) Reed, W. L., and Cone, W. V.: Mechanism of Fixed Dilatation of Pupil Resulting from Ipsilateral Cerebral Compression, J. A. M. A. **112**:2030-2034 (May 20) 1939. (*g*) Spiller, W. G.: Tumor Malformations of the Central Nervous System, Rev. Neurol. & Psychiat. **6**:677-682, 1908; cited by Cushing, H.: Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917.

be served by tracing the chronological development of present conceptions of the mechanisms for production of false signs; but it is of interest to note that the mechanisms having to do with gross brain displacement, which were apparently given small consideration at the time of Collier's publication, now appear, together with herniation of the uncus through the tentorial notch, to be of major importance, along with infarction at a distance and possibly hydrocephalus, edema and gliosis.

- General compression of a nerve having a long course.[5a]
- Meningitis [3]
- Edema and gliosis [6]
- Metastatic deposits.[3]
- Degeneration of dorsal columns [7]
- Infarction at a distance
  - Occlusion of vessel by neoplasm [3]
  - Occlusion by herniation through dural aperture [8]
- Hydrocephalus [9]
- Transmitted pressure
  - Due to herniation of a part through a dural aperture [10]
  - Without herniation of a part [11]
- Gross brain displacement [12]
  - Brain stem shifted in sagittal plane
    - Traction on cranial nerves [3]
    - Kinking of cranial nerves over vessels [5a]
  - Brain stem shifted to the side [13]
    - Tentorial notching [14]
    - Rim of foramen magnum pressure [5b]
    - Points of emergence of cranial nerves.[15]
    - "Distortion" of corticospinal tract [5b]

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6. Collier.[3] Nielsen.[1] Rand and Halsey.[2b]

7. Batten, F. E., and Collier, J.: Spinal Cord Changes in Cerebral Tumor, Brain **22**:473, 1899. Collier.[3]

8. Meyer.[5e] Reed and Cone.[5f]

9. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940. Collier.[3]

10. Cushing.[5a] Rand and Cone.[5f]

11. (*a*) Cushing, H.: Some Aspects of the Pathological Physiology of Intracranial Tumors, Boston M. & S. J. **161**:71-80, 1909. (*b*) David, M.: De l'atteinte unilatérale et homolatérale du trijumeau au cours de certains méningiomes parasagittaux. Des erreurs de localisation qui peuvent en résulter, Rev. neurol **73**:628-630, 1941.

12. Bruns, L.: Die Geschwülste des Nervensystems: Hirngeschwülste; Rückenmarks- und Wirbelgeschwülste; Geschwülste der peripheren Nerven, Berlin, S. Karger, 1908; cited by Cushing.[5a]

13. (*a*) Cushing, H.: Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle, Philadelphia, W. B. Saunders Company, 1917. (*b*) Grey.[5c] Spiller.[5g]

14. Collier.[3] Kernohan and Woltman.[5d]

15. Wernicke, cited by Cushing.[5a]

REPORT OF CASE

It was my recent privilege to observe a false sign concerning the explanation of which no certain statement can be made, but one about which certain speculations are possible.

Paralysis of the left trigeminal nerve; increased intracranial pressure; displacement of the calcified pineal body to the left. Negative results of burr hole exploration for subdural hematoma in the right parietal region. Ventriculography followed by removal of a meningioma at the pterion on the right.

J. M. P., a 40 year old power shovel operator, was first seen Jan. 3, 1949, with the complaint that he awoke on the morning of the day before with a feeling of numbness over the entire left side of his face and scalp. In response to questioning, he related that he had noticed the onset of a mild suboccipital headache in June or July 1948. These headaches sometimes extended into both temporal regions, but lately they had been less severe than at the onset and he had come to disregard them. At about the time the headaches began he noted tinnitus in the left ear, and this remained pretty much unchanged. The patient had been working up to the day before he was admitted for examination.

The neurological examination disclosed papilledema in both eyes, with an elevation of 2 D. on the right and of 6 or 7 D. on the left. The right pupil reacted sluggishly to light but was of equal size with the left. The corneal reflex was diminished on the left. Sensation to touch was absent in the ophthalmic and maxillary distributions of the left trigeminal nerve and was moderately reduced in the mandibular division. Pain appreciation was practically absent in the ophthalmic and maxillary divisions but was only slightly diminished in the mandibular division. There was complete paralysis of the left masseter, temporalis and pterygoid muscles. A questionable Babinski response was present on the left. The neurological examination, including gross testing of the visual fields, revealed an otherwise normal status. Roentgen examination of the skull showed a pronounced degree of displacement of the calcified pineal body to the left, with enlargement of the sella turcica and thinning of the posterior clinoid processes.

There could be no question that the space-taking mass lay on the right side of the head contralateral to the manifest indications of the cranial nerve paralysis, and it was thought probable that a space-taking mass which would so gently compress the right hemisphere as not to produce signs more definite than a questionable Babinski response on the left and yet shift the upper brain stem so immoderately to the opposite side as to produce the trigeminal palsy would be a subdural hematoma. Accordingly, burr hole exploration, to be followed by ventriculography if hematoma was not encountered, was advised.

On January 10, with the use of local anesthesia, a burr hole was made in the right parietal region, through which the brain bulged decidedly. Since no other local abnormality was present, bilateral burr holes were made in the posterior parietal area, in the usual locations, and the ventricles were tapped. The initial pressure within the ventricles was 19 cm. of fluid. Fluid was replaced with air; a catheter was placed in the ventricle and clamped shut with an instrument, and ventriculograms were made. These revealed good filling of both lateral ventricles and the third ventricle, with a shift of all three to the left side. The right lateral ventricle displayed a flat top characteristic of migration beneath the falx, and the third ventricle shadow was inclined to the left. This and the other views led

to the diagnosis of a space-taking lesion in the right temporal region. The patient was returned to the operating room, where a five hole osteoplastic flap was turned down through tissues which were excessively vascular. Through the unopened dura an area of abnormality was seen over the posterior inferior portion of the right frontal lobe; and as soon as the dura was opened over this site of a suspected lesion approximately 1 ounce (30 cc.) of soft, mushy tumor extruded spontaneously. Quick examination of sections revealed a meningioma, and total removal of the tumor, which weighed 48 Gm. and which had its origin at the pterion, was accomplished.

The patient was last examined on Feb. 1, 1949, at which time the edema of the right disk had almost disappeared and the elevation of the left disk was much less than before. A slight degree of weakness persisted about the left side of the mouth. No abnormality was apparent in the visual fields. There still existed complete paralysis of the muscles innervated by the motor branch of the left trigeminal nerve, but there had been complete return of sensation to the face, and the corneal reflexes were equal.

In search of an explanation of the process responsible for the trigeminal paralysis in this case, reports of similar cases were sought. Paralytic and irritative disturbances of the trigeminal nerve contralateral to tumors of the posterior fossa have been described,[16] as have instances of trigeminal paralysis on the same side as, but at some distance from, tumors of major chambers.[16a] No report of paralysis of the fifth cranial nerve on the side opposite a tumor of a major chamber was found. Certain features of the case reported, such as the fundamental nature of the tumor present, the paucity of neurological findings and the early recovery of function of the trigeminal nerve after removal of the tumor, make it possible to eliminate many of the mechanisms listed in the tabulation. The mechanisms having to do with herniation of a part through the tentorial hiatus and the mechanisms operating in the presence of gross displacement of the brain stem in a lateral direction merit more consideration.

Because of the extremely well protected position of the portion of the trigeminal nerve between its superficial origin on the pons and its entrance into Meckel's cavity, and because this patient did not have pyramidal tract signs on the right side attributable to notching of the brain stem by the tentorium, it seems reasonable to exclude the mechanism of direct pressure on the trigeminal root by the side of the shifted pons, either at the point of emergence from Meckel's cavity or more proximally. Since there was no involvement of the third cranial nerve, it is possible to forego any further consideration of pressure on the fifth nerve by a herniated portion of the under surface of the temporal lobe.

16. Cushing.[13a] Hamby, W. B.: Trigeminal Neuralgia Due to Contralateral Tumors of the Posterior Cranial Fossa, J. Neurosurg. **4**:179-182, 1947.

16a. Cushing.[11a] Collier.[3]

The problem is thus narrowed down to that of explaining a paralysis of the trigeminal nerve on the side to which the brain stem was shifted; in so doing, the gross displacement of the brain is considered, but something in addition to the normal anatomic relations is required.

A variety of vascular variations in the region of the trigeminal root have been described by Sunderland.[17] He has found that the superior cerebellar artery in its course to the cerebellum sometimes loops downward to make firm contact with the upper surface of the trigeminal nerve, which it may indent, or the vessel may actually perforate the sensory root of the nerve. The posterior inferior cerebellar artery has been seen to extend superiorly and groove the under surface of the trigeminal nerve. On occasion the basilar artery has been found to arch far to the side and compress the medial margin of the sensory root. In three of 210 specimens there was found, always on the left side, a large anastomotic arterial vessel connecting the basilar artery with the intracavernous portion of the internal carotid artery. In two of the three specimens this anastomotic vessel ran into Meckel's cavity in company with the trigeminal nerve. In all three instances the anastomotic artery was the largest branch of the basilar artery, being twice the diameter of the superior cerebellar artery; and it was considered by Sunderland that the artery served as a means of delivering blood from the internal carotid artery into the basilar artery system, since all three specimens showed exceedingly small vertebral arteries. With these possibilities of intimate relations between the trigeminal root and major intracranial vessels existing, it is possible to explain the trigeminal paralysis in the case reported along much the same lines as one does the optic nerve atrophy in certain instances of infrachiasmatic tumor in which the optic nerves are displaced superiorly so strongly as to come into contact with, and be grooved by, the anterior cerebral arteries.[5n]

The suggested explanation of the trigeminal paralysis in the case reported is that this trigeminal nerve was crossed by or perforated by an arterial vessel of sufficient size that grooving of the nerve, with functional failure, occurred when the side of the upper pons was shifted against these structures and the resistant lateral wall of the posterior chamber.

SUMMARY

"False" localizing signs associated with intracranial tumor are so designated because of the interpretation put on them, since they actually indicate abnormality at their respective sites, but produced by processes acting at some distance from the tumor.

17. Sunderland, S.: Neurovascular Relations and Anomalies at the Base of the Brain, J. Neurol., Neurosurg. & Psychiat. **11**:243-257, 1948.

"False" signs occur with greater frequency late in the course of intracranial tumor, and after generalized increase in intracranial pressure is established.

A number of important mechanisms producing "false" signs have been described since the appearance of the first publication dealing specifically with these signs.

A case is reported of a patient with paralysis of the left trigeminal nerve due to a meningioma of the right cerebral hemisphere.

The suggested explanation for the trigeminal paralysis reported is that the left trigeminal nerve was penetrated by, or crossed by, a large arterial vessel which grooved and locally compressed the nerve when the upper brain stem was shifted against the nerve-artery combination.

A MULTIPLE CHOICE TYPE OF THE VISUAL RETENTION TEST

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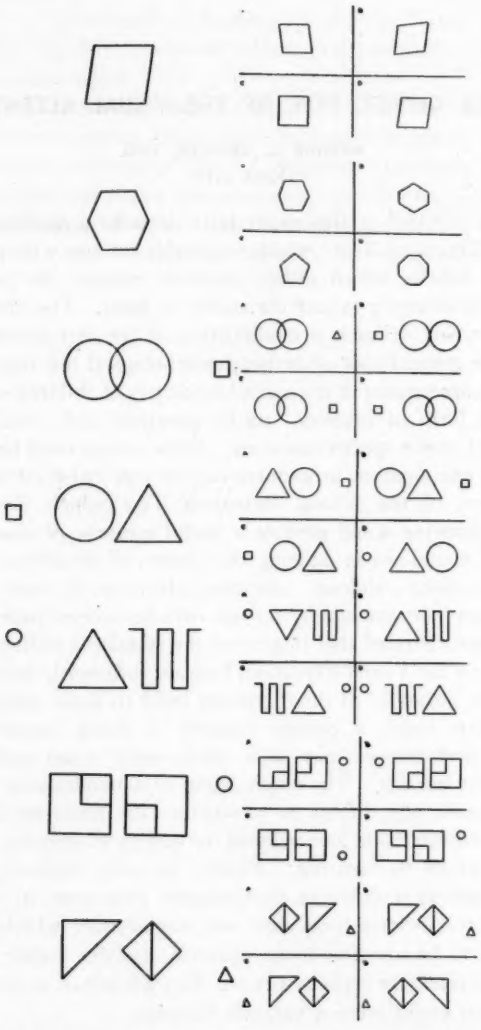
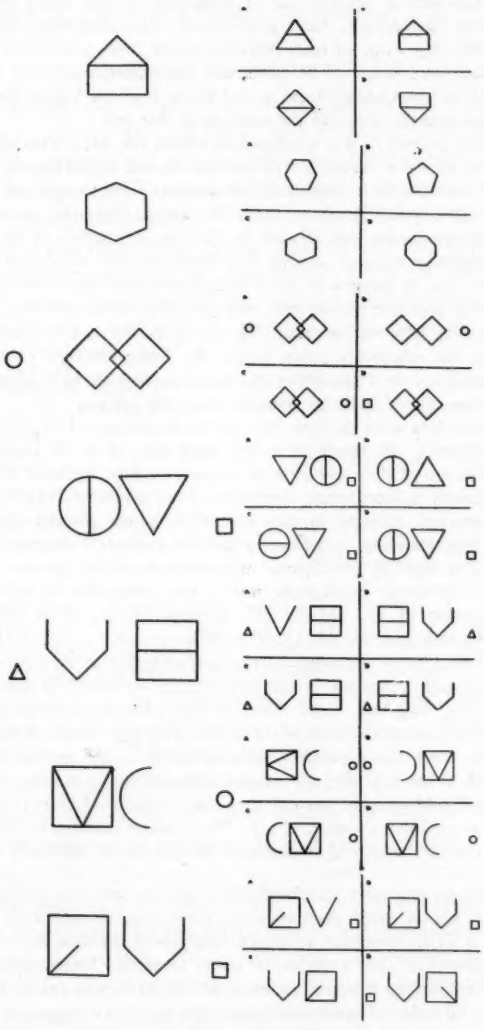
THE PURPOSE of this paper is to describe a modification of the Visual Retention Test [1] which is suitable for use with patients who have motor deficits which either preclude entirely the possibility of drawing or significantly impair the ability to draw. The initial stimulus for the contriving of such a modification of the test arose within the setting of the general task of devising psychological test methods appropriate for the assessment of the mental capacities of children with cerebral palsy in the form of bilateral spastic paralysis and, usually, marked impairment of motor speech functions. Since a keen need for adequately standardized examination procedures of this type exists, it was felt that a modification of the Visual Retention Test which eliminated the necessity of drawing could provide a useful measure of visual retentive capacity that would aid in defining the pattern of intellectual assets and limitations in these children. Another advantage of such a modified form of the test is its availability for use with hemiplegic patients. While it has been demonstrated that in general the standards utilized in scoring performance on the Visual Retention Test are sufficiently lenient to allow a patient with paralysis of the dominant hand to draw adequately with the subordinate hand, a certain element of doubt concerning interpretation of performance may arise occasionally when such a patient does poorly on the test. The employment of a nondrawing type of the test could resolve any doubts as to whether the necessity for drawing with the subordinate hand had reduced the quality of drawing to a degree sufficient to affect the scoring. Finally, in some brain-injured, nonhemiplegic patients a defective performance may seem to be attended with such motor awkwardness that one may wonder whether the deficiency is not to be ascribed to an apractic disorder rather than to an impairment in retentive capacity per se. In such instances a nondrawing type of the test could serve a valuable function.

From the Department of Psychology, State University of Iowa.

1. (*a*) Benton, A. L.: A Visual Retention Test for Clinical Use, Arch. Neurol. & Psychiat. **54**:212-216 (Sept.) 1945. (*b*) Benton, A. L., and Collins, N. T.: Visual Retention Test Performance in Children: Normative and Clinical Observations, ibid. **62**:610-617 (Nov.) 1949.



Cards 1 to 7 of the multiple choice type of the Visual Retention Test, with corresponding designs of the drawing type of the test.



Cards 8 to 14 of the multiple choice type of the Visual Retention Test, with corresponding designs of the drawing type of the test.

METHOD

Various "multiple choice" cards were constructed, each of these cards containing four more or less similar designs, one of these four designs being identical with a Visual Retention Test design. After preliminary experimentation, which served to establish the difficulty value of each multiple choice card, a selection of cards was made, and a definitive series of 14 cards was assembled, each card corresponding to one of the 14 designs of both Form A and Form B of the Visual Retention Test.[2] The figure illustrates the cards of the multiple choice test.

The following procedure was employed in giving the test: The subject was told that he would be shown a design for 10 seconds, during which time he was to study it carefully. It would then be removed, and another card, containing four more or less similar designs, would be shown him. He was to designate, either by pointing or by naming (each design was labeled *A, B, C* or *D*), which of the four designs was the one originally exposed to him. The basic designs, which were exposed for 10 seconds, were the 14 designs of the Visual Retention Test. After each exposure the corresponding multiple choice card was presented to the subject. The average administration time was six minutes. The score on the test was the sum of the correct choices, the maximum score being 14. Since multiple choice test items of this sort permit a 1 in 4 possibility of chance success on each item, it is evident that scores of less than 5 indicate virtually complete failure.

The normative data were derived from the performances of 94 subjects of varied grades of intelligence, the range of whose ages was 15 to 47 years.[3] Care was taken in the selection of these subjects to insure that none suffered from a recently acquired impairment of intellectual function or was psychotic. The histories of the intellectually retarded subjects in this normative group showed clearly that the deficit was of long standing, and hence either congenital or acquired in the early years of life. The level of intelligence was defined on the basis of performance on the Wechsler-Bellevue intelligence test. Four categories of intelligence were established: superior (I. Q., 110 to 128), average (I. Q., 85 to 109), subnormal (I. Q., 70 to 84) and defective (I. Q., 50 to 69).

The clinical data were provided by the performances of 30 patients who were under evaluation and treatment in the neurological or neurosurgical departments of the University Hospitals, Iowa City, or the neuropsychiatric service of the Des Moines Veterans Administration Hospital. The age range of this group was 19 to 49 years. Only those patients were included in the group whose history, particularly with respect to the educational and vocational status, and pattern of psychological test performance insured that their premorbid or pretraumatic intellectual level was at least average (I. Q., 85 or above) and who presented clear evidence of a recently acquired impairment in behavioral efficiency ascribable to

2. Originally an extensive standardization was carried out, utilizing two series of seven multiple choice cards, each series corresponding to one of the forms of the Visual Retention Test. However, statistical analysis of the data indicated an inadequate "retest reliability" for a series of seven multiple choice cards, and a new standardization employing a single series of all 14 cards was made. The relatively low reliability of a series of seven multiple choice cards, as compared with a series of the same number of designs to be drawn, is due to the possibility of chance success which any multiple choice test offers, and which can be counteracted only by increasing the number of test items.

3. The use of a lower age limit of 15 years in this normative "adult" group is fully justified by previous findings [1b] that, as a group, 15 to 16 year old children do quite as well on the Visual Retention Test as do adults.

cerebral damage, this evidence being derived from both final clinical evaluation and the pattern of psychological test performance. The degree of impairment is probably best designated as "moderate." All the patients were "rational"; none had shown psychotic reactions, and none showed a generalized organic defect state with gross impairment of behavioral efficiency. On discharge from the hospital, all returned home.

NORMATIVE AND CLINICAL DATA

Table 1 shows the distribution of test scores for the normal and clinical groups. Inspection of these data indicates that the test is an "easy" one for unimpaired persons of normal intelligence. Of the 65 subjects of average intelligence or higher, only one made a score of less than 10, i. e., made more than 4 errors on the 14 designs. Perfect performances were not rare, being made by about one fourth of the subjects in the superior group and by about one tenth of the subjects in the average group. Perfect or near-perfect performance (1 error or less) was made by a majority of subjects in the superior group and by

TABLE 1.—*Distribution of Scores on the Multiple Choice Type of Visual Retention Test*

Group	Number of Subjects	Score										Mean Score	Median Score
		2-5	6	7	8	9	10	11	12	13	14		
Superior (I. Q. 110-128).....	19	..	..	..	..	..	..	3	4	7	5	12.7	13
Average (I. Q. 85-109).....	46	..	..	..	..	1	6	9	13	12	5	12.0	12
Subnormal (I. Q. 70-84).....	13	..	2	..	1	5	..	1	3	..	1	9.7	9
Defective (I. Q. 50-69).....	16	3	5	2	2	2	..	..	1	1	..	7.1	6.5
Acquired impairment.....	30	3	2	2	8	1	4	3	3	3	1	9.0	8.5

approximately three eighths of the subjects in the average group. In contrast, the typical performance of the defective group (I. Q., 50 to 69) was poor, only two of the 16 making a score of 10 or better. As might be anticipated, the moderately subnormal group (I. Q., 70 to 84) occupied a "borderline" position in the distribution of scores. About half the subjects in this group performed on a clearly defective level, while the performances of the other half were within the normal range.

Of the 30 patients of average intellectual endowment or better who were judged to be suffering from an acquired impairment of behavioral function referable to a cerebral lesion, it was found that about half the patients in this group (53 per cent) made clearly defective performances (i. e., a score of less than 10) on the test. Moreover, there seemed to be a tendency for those performances which were in the normal range to cluster in the lower half of the range (scores 10 to 11). Nevertheless, perfect and near-perfect performances did occur, being made by four patients in the total group of 30. Given groups whose original intellectual endowment is average or better, the degree of differentiation between impaired and unimpaired subjects afforded by the test may be expressed

as follows: If a nonpsychotic subject of this intellectual caliber makes a score of less than 10 on the test, the probability of his being impaired is very high, since only about 2 per cent of unimpaired subjects make such scores. On the other hand, if such a subject makes a score of 10 or better, no important conclusions can be drawn, since substantial numbers of both unimpaired and impaired subjects make such scores. It is evident that in this context a score of less than 10 is more meaningful clinically than a score of 10 or more.

Retest Reliability.—The reliability of the multiple choice form, determined by the "split-half" method, with correction for the full length of the test, was found to be 0.76. The standard error of measurement was 1.40.[4]

TABLE 2.—*Schema for Interpretation of Performances on the Visual Retention Test (Adult Norms)*

Performance Level	Score		
	Multiple Choice Type	Form A or Form B Drawing Type	Total Score, Form A and Form B, Drawing Type
Superior	14	..	14
High average	13	7	13
Average	12	6	12
Low average	11	5	11
Dull average	10	.	10
Borderline	9	4	8-9
Defective	8	3	7
	7	..	6
	6	2	4-5

Interpretation of Performance.—A schema for the interpretation of scores on the multiple choice type of the Visual Retention Test, together with equivalent scores on the drawing type of the test, is presented in table 2. This schema is based not only on the normative findings reported above but also on the extensive data collected in a preliminary study involving a direct comparison of performance of the same subjects on the two types of the test.[2] The schema may be applied to the interpre-

4. Concretely, this statistic indicates that, given an obtained score (e. g., 10), there are 85 chances in 100 that the "true" score, unaffected by adventitious influences, lies between the limits of 2 points on either side of the obtained score (e. g., between the limits of 8 and 12). This may be compared with the reliability of either form of the drawing type of the Visual Retention Test, in which the reliability coefficient has been found to be 0.71, with a standard error of measurement of 0.94. A standard error of measurement of this magnitude indicates that in practice there are 71 chances in 100 that the obtained score does not deviate from the "true" score by more than 1 point and 97 chances in 100 that the two scores do not deviate by more than 2 points.

tation of the performances of subjects over the age of 12 years. Interpretation of the performances of younger children may be made by utilizing the schema in conjunction with previously published norms on the performances of children in the age range of 8 to 12 years.[1b]

COMMENT

The normative and clinical findings suggest that this brief multiple choice visual retention test is able to demonstrate impaired function in some patients in whom the fact of impairment is not particularly obvious and in whom the degree of impairment is moderate. That unimpaired adults find the test an easy one is indicated by the absence of poor scores in the normative groups of adequate intelligence. This fact, of course, facilitates interpretation of poor performance. In the group of impaired patients, test performance was significantly poor in about half the group. Two comments concerning the observation that the test did not reflect the fact of impairment in 50 per cent of the patients may be made.

First, the test may be said to have "failed" to disclose impairment in these patients only if one assumes that behavioral impairment consequent to cerebral injury is always of a general nature. Most psychological test methods currently utilized for disclosing impairment seem to be based on the implicit assumption of a general impairment extending over all behavior. But the assumption is hardly supported by clinical neurological observation, which, on the contrary, testifies to the variety rather than the unity of behavioral defects in organic impairment states. The idea of diversity, rather than uniformity, in impairment is further supported by recent psychological studies [5] which have demonstrated that the Wechsler-Bellevue Deterioration Ratio and the Shipley-Hartford Conceptual Quotient, two methods enjoying extensive use for disclosing "general impairment," show no significant correlations with each other when applied to the same patients. The defining conditions in behavioral impairment may be the sensory modality affected (e. g., tactual defects versus visual defects), the type of the task (e. g., retention versus abstract reasoning) or the content of the task (e. g., verbal versus numerical). Every clinician has seen examples of behavioral defect limited to one or another area. Of course, generalized defect and combinations of defects do occur, but the point must be made that there is no necessity for their occurrence, as compared with specific and uncombined defect, despite the insistence of some theorists that the impairment extends to all fields of behavior and despite their attempts to apply a

5. Garfield, S. L., and Fey, W. F.: A Comparison of the Wechsler-Bellevue and Shipley-Hartford Scales as Measures of Mental Impairment, J. Consult. Psychol. **12**:259-264 (Aug.) 1948. Magaret, A., and Simpson, M. M.: A Comparison of 2 Measures of Deterioration in Psychotic Patients, ibid. **12**:265-269 (Aug.) 1948.

single, unitary principle, such as "categorical behavior" or "synthetic capacity," to every aspect of a patient's behavior.[6] Moreover, the fact of specificity is often utilized for diagnostic purposes. It would seem that a more fruitful goal of the psychological examination would be to determine the nature of the behavioral deficit, if present, and not to ascertain whether and to what degree the patient is "impaired" in general. The question to be posed, then, concerns the way in which the patient is impaired, and not merely whether he is impaired or not.

Viewed from this standpoint, the fact that performance on the Visual Retention Test is adequate in many patients who show one type of behavioral impairment or another means simply what the findings indicate, i. e., that these patients do not show a deficit in immediate visual memory functions. Full exploitation of the clinical significance of this finding (as with most other psychological findings in nervous disease) waits on systematic and critical investigation. Unselective observation to date suggests that the site of the lesion is of decisive importance in determining whether or not a patient will show defective performance on the test. Patients with parieto-occipital lesions typically show impaired performance[7] on the Visual Retention Test, while patients with frontal lesions typically do not.[8]

The second comment is that many psychological test methods currently in use which seem to identify behavioral impairment referable to a cerebral lesion in the majority of such cases actually do not possess great efficiency in discriminating between clinically impaired and unimpaired persons. They succeed in "identifying" organic behavioral

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6. These unitary principles, which seem eminently "reasonable" and "congruent" at first glance, have found a ready acceptance in psychoneurology. But after examination of their evidential basis and predictive value, one is inclined to concur with the criticism of D. O. Hebb (Man's Frontal Lobes: A Critical Review, Arch. Neurol. & Psychiat. **54**:10-24 [July] 1945) that these generalizations "explain at once too much and too little. They are too broad and ill defined to be meaningful, and they are too likely to lead to an *ad hoc* interpretation of symptoms. The attractiveness or plausibility of such formulations is part of their danger; it is too easy to think of all the facts they account for and not to ask whether there are others which they do not explain or whether symptoms are absent which they require."

7. Bender, M. B.: Polyopia and Monocular Diplopia of Cerebral Origin, Arch. Neurol. & Psychiat. **54**:323-338 (Nov.-Dec.) 1945. Bender, M. B.; Wortis, S. B., and Cramer, J.: Organic Mental Syndrome with Phenomena of Extinction and Allesthesia, ibid. **59**:273-291 (March) 1948. Bender, M. B.; Furlow, L. T., and Teuber, H. L.: Alterations in Behaviour After Massive Cerebral Trauma (Intraventricular Foreign Body), Confinia neurol. **9**:140-157, 1949. Benton.[1a]

8. Ackerly, S. S., and Benton, A. L.: Report of Case of Bilateral Frontal Lobe Defect, in The Frontal Lobes, A. Research Nerv. Ment. Dis., Proc. **27**:479-504, 1947. Mettler, F. A.: Selective Partial Ablation of the Frontal Cortex, New York, Paul B. Hoeber, Inc., 1949.

impairment only at the cost of evaluating an embarrassingly high proportion of normal subjects as "impaired." This fact is usually not brought very forcibly to the attention of the practicing clinician, since in his work he is not likely to have occasion to evaluate any sizable number of control subjects but, rather, is called on to assess a selected group in which the probability of impairment is relatively high. That explicit or implicit assumptions concerning the level of performance to be expected of a normal subject are often seriously in error has been demonstrated on an empirical basis repeatedly.[9] The present communication is hardly the place to present a detailed critical evaluation of the diagnostic efficacy of the various psychological test methods in current use. It is probably fair to say that the results of such an assessment would be to indicate that none possesses any greater efficacy in differentiating impaired and unimpaired patients "in general" than does the Visual Retention Test. In the light of the preceding discussion, it is probable that no single test method is likely to achieve very impressive efficiency in this regard.

9. Pearson, G. H. J.; Alpers, B., and Weisenburg, T. H.: Aphasia: A Study of Normal and Control Cases, Arch. Neurol. & Psychiat. **19**:281-295 (Feb.) 1928. Benton, A. L.: A Study of the Performances of Young Adults on the Kohs Block Designs Test, J. Appl. Psychol. **25**:420-427 (Aug.) 1941. Hebb.[6]

LATERAL SPINOTHALAMIC TRACTOTOMY FOR RELIEF OF PAIN IN CAUDA EQUINA INJURY

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LATERAL spinothalamic tractotomy, introduced by Spiller and Martin [1] in 1912, has been of immeasurable benefit to patients with intractable pain below the level of the fourth or fifth dermatome. The operation has found its greatest usefulness in patients with pain caused by malignant growths.[2] More recently, because of the growing incidence of traumatic paraplegia, it has been suggested as a method of relieving the pain that accompanies spinal cord injuries. These lesions were common during the war as a result of gunshot and shrapnel wounds and are now seen in increasing frequency because of injury following traffic and mining or other occupational accidents.

Lateral spinothalamic tractotomy has proved successful in relieving the discomfort of patients with pain following injuries to the cauda equina. This type of injury frequently causes intractable pain.

Almost without exception, injury to the caudal roots results in intractable pain, sufficiently severe to arrest all efforts at rehabilitation, which must be the ultimate goal in the treatment of paraplegia. It is the purpose of this paper to present a series of 11 cases of trauma to the cauda equina with resultant partial or complete paraplegia in which relief of pain was obtained by bilateral spinothalamic tractotomy.

Cauda equina pain is excruciating, sharp, and radiates along the distribution of the nerve roots. It is persistent but varies in intensity.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Spiller, W. G., and Martin, E.: Treatment of Persistent Pain of Organic Origin in the Lower Part of the Body by Division of the Spinal Cord, J. A. M. A. **58**:1489-1490 (May 18) 1912.

2. Crutchfield, W. G.: Neurosurgical Procedures for the Relief of Pain in Advanced Cancer, Radiology **45**:253-257 (Sept.) 1945.

The increase in intensity of pain at night resembles the pain seen in the presence of tumors of the cauda equina. The pain is not diffuse. On being questioned superficially, the patient with a lesion of the cauda equina will complain of burning pain. When questioned more specifically, he will invariably explain that the pain is as that of some one placing "a red hot iron" on a nerve in his leg. The diffuse burning pain which most paraplegic patients with higher injuries experience does not follow any root distribution and may be due to vascular disturbances. Cauda equina pain actually follows the distribution of one or more roots and can readily be distinguished as a distinct pain pattern. Studies now being conducted indicate that patients with this type of pain invariably develop a high threshold for perception of pain, as well as a high threshold for reaction to pain. Quantitative measurements of these factors with the Wolff-Hardy machine strongly point to the organic origin of cauda equina pain.[3]

The facies dolorosa in the presence of cauda equina pain conforms to the classic concept, and the mental changes in the affected patients follow a characteristic pattern. Introversion, negativism with suicidal tendencies and extreme flattening of affect are common. Relief of pain is mandatory in order that morphine addiction, alcoholism or a major post-traumatic psychosis may be averted. As particularly stressed by Freeman and Heimburger,[4] the administration of habit-forming drugs for the relief of pain due to injury of the spinal cord can no longer be permitted, since modern treatment of paraplegia has lengthened the life expectancy. Only complete freedom from pain will permit the patient to rehabilitate himself physically and mentally. This desirable relief from pain must be accomplished early after injury. The lack of appreciation among members of the medical profession of the mandatory need of rehabilitation for paraplegic patients has surrendered many of these patients to the tragedy of drug addiction and alcoholism. The case of a young medical officer who received an injury to the cauda equina during the war and who refused surgical intervention for the relief of pain is only one of many instances. This young physician died four years after the injury, having been useless to himself, to his family and to society because of the sequelae of extreme morphine addiction.[5]

In the majority of instances, attempts to relieve pain by lysis of the caudal roots, by posterior rhizotomy or by lumbar sympathectomy have failed, although temporary improvement may be noted. Freeman and

3. Hazouri, L. A., and Meirowsky, A. M.: Unpublished data.

4. Freeman, L. W., and Heimburger, R. F.: Surgical Relief of Pain in Paraplegic Patients, Arch. Surg. **55**:433-440 (Oct.) 1947.

5. Meirowsky, A. M.: Personal communication to the author.

Clinical Data on Eleven Cases of Intractable Pain Due to Injury of the Cauda Equina Relieved by Lateral Spinothalamic Tractotomy

Name	Date and Nature of Injury	Onset of Pain	Location of Pain	Type of Pain	Previous Operative Relief Measures	Preoperative Bladder Status	Preoperative Loss of Sensation	Preoperative Motor Loss Below Level of Injury	Date of Chordotomy	Post-operative Bladder Status	Post-operative Level of Analgesia	Increased Motor Loss	Follow-Up Interval Loss of Pain
B. F.	9/44 Gunshot wound	9/44	Left inguinal region; left lower extremity	Sharp, intermittent radicular pain	Injection Th 10 root	Capacity, 350 cc.; residual, 41 cc.	Left: below Th 12, including genitalia; right: hypesthesia below L 2, anesthesia below L 3	Incomplete below Th 12	4/13/49	Capacity, 325 cc.; residual, 0	Below Th 7 bilaterally	No	3 mo. 75%
J. H.	12/47 Auto accident	About 3/48	Right hip; burning intermittent in left lower extremity	Intermittent root type of pain	Nerve block L 1 and L 2 on left with procaine and alcohol; exploratory laminectomy	Automatic bladder	Below Th 12 bilaterally	Complete below Th 12	12/3/48	Automatic bladder; no residual urine	Below Th 2 bilaterally	No	15 mo. 100%
C. S.	4/46 Auto accident	Time of fusion	Both heels and feet	Severe cauda equina pain, both extremities	Lumbar sympathectomy	Voiding without residual urine	Below L 3 bilaterally	Complete below L 3	9/29/48: Th 1 and Th 2* 12/6/48: Th 2 and Th 3	Capacity, 150 cc.; residual, 0	Below Th 7 bilaterally	No	15 mo. 100%
A. H.	Gunshot wound 2/45	About 2/45	Right knee; dorsum of both feet	Sharp, shooting root pain, especially on right	Laminectomy; sympathetic blocks	No residual urine	Below L 3 bilaterally	Partial below Th 12; complete below L 3	7/23/48	No change	Below Th 4 on right and Th 5 on left	No	12 mo. 100%
J. O.	12/44	2 weeks after injury	Lower extremities	Severe, lancinating radicular	Bilateral chordotomy; laminectomy	300 cc. voided; no residual urine	Below L 3 bilaterally	Complete below L 3	5/31/49	None done	Below Th 3 on left and Th 4 on right	No	2 mo. 100%
B. P.	5/48	About 8/48	Persistent cauda equina pain	Shooting pain	Laminectomy; posterior rhizotomy; lumbar sympathectomy	Capacity, 480 cc.; residual, 475 cc.	Below L 1, incomplete on left and complete on right	Complete below L 1	12/22/48	No change	Below Th 5 bilaterally	No	13 mo. 100%
J. W.	4/49 Gunshot wound	5/49	Left lower extremity	Radiating pain in legs constant	None	Automatic bladder; no residual urine	Below Th 12 bilaterally	Complete below Th 12	10/3/49	Automatic bladder; no residual urine	Below Th 5 bilaterally	No	5 mo. 85%
R. N.	4/45 Gunshot wound	5/45; more severe since 1/49	Legs	Sharp, radiating pain	Laminectomy	Suprapubic catheter; straight drainage	Below Th 12 bilaterally	Incomplete below L 1 on right and complete below L 1 on left	7/29/49	Suprapubic catheter; straight drainage	Below Th 6 bilaterally	No	7 mo. 95%
R. M.	3/49	Time of injury; severity increased progressively	Posterior aspect of thighs and inner surface of legs	Sharp, shooting root pain	Laminectomy Th 12—L 1; scar resection	Capacity, 150 cc.; none voided	Below L 2 on right and below L 3 on left	Complete below L 1 on right and below L 2 on left	11/14/49	Capacity, 335 cc. residual urine, 25 cc.	Below Th 6 bilaterally	No	3 mo.; incomplete relief of pain† 75%
H. C.	2/49	2/49	Lower extremities	Sharp, shooting pain; coldness of legs	None	Automatic bladder	Below L 1 bilaterally	Complete below Th 12	11/10/49	Functioning automatic bladder	Below Th 7 on left and Th 10 on right	No	3 mo.; incomplete relief of pain† 75%
L. T.	Hyperextensive injury (1943); HNP removed (1946); venous angioma (1948)	3/49	Legs	Intractable radicular pain, at lower extremities	Decompressive laminectomy	No residual urine	Below Th 10 bilaterally	Partial below L 1	6/15/49	No residual urine	Below Th 6 bilaterally	No	3 mo. 90%

* Patient became hysterical on operative table, and the first operation was not fully completed. Second operation, at a later date, was successful.
† Operative result poor, but psychiatric problems may be responsible.

Heimburger,[4] Woodhall[6] and, more recently, Munro[7] have suggested lateral spinothalamic tractotomy for the relief of cauda equina pain. Study of the results obtained at Kennedy Hospital has tended to confirm their opinion. We at this hospital do not believe the operation should be deferred once the pain has become a permanent feature and threatens the success of physical and mental rehabilitation. Data on the present series of 11 cases of cauda equina pain, relieved by lateral spinothalamic tractotomy, are summarized in the accompanying table. The typical intractable root pain was present in all 11 cases. All the patients were treated by bilateral section of the spinothalamic tract, which was performed in the region of the first and second thoracic roots. The incision was made to a depth of approximately 5 mm., with the knife emerging 2 mm. anterior to the point of exit of the anterior roots.[4] Severance of the dentate ligament bilaterally prior to tractotomy, as recommended by Kahn and Peet,[8] in order to allow safe rotation of the cord, has been of the greatest technical value in carrying out the operative procedure satisfactorily. All operations were performed with the use of local anesthesia, which permitted a check on the sensory level during the operative procedure. In two cases a second operation was required. In one case operation had been performed in this clinic, and in the other chordotomy had been done elsewhere. Failure in the case in which the original operation was performed at Kennedy Hospital was due to the use of preanesthetic drugs, which caused mental confusion in the patient. This confusion masked the sensory response so much that the patient's level of analgesia could not definitely be established at the time of operation. The result was excellent after the second operation. All 11 patients were relieved of the pain. There was no further increase in motor loss in the patients with partial paraplegia. The bladder status was unaltered after operation.

REPORT OF A CASE

A representative case is reported in detail.

A. H., a white veteran aged 23, received a gunshot wound of the cauda equina while serving with the Marines in the Pacific theater. Immediately after the injury the patient lost motor power and sensation in the lower extremities. Two weeks after the injury a suprapubic cystostomy was performed. About one month later some sensory perception and motor power began to return. At that time the patient

6. Woodhall, B., in discussion on McCravey, A.: War Wounds of Spinal Cord: Plea for Exploration of Spinal Cord and Cauda Equina Injuries, J. A. M. A. **129**:152-153 (Sept. 8) 1945.

7. Munro, D.: Two-Year End-Results in the Total Rehabilitation of Veterans with Spinal Cord and Cauda Equina Injuries, New England J. Med. **242**:1-16 (Jan. 5) 1950.

8. Kahn, E. A., and Peet, M. M.: The Technique of Anterolateral Cordotomy, J. Neurosurg. **5**:276-283 (May) 1948.

* Patient became hysterical on operative table, and the first operation was not fully completed. Second operation, at a later date, was successful.
† Operative result poor, but psychiatric problems may be responsible.

first noticed burning pain in both feet. In June 1945 a laminectomy was performed, but the operative findings are not available. In October 1945 the patient underwent a transurethral resection and simultaneous closure of the cystostomy. Since that time the patient has been able to void without residual urine. Sensory and motor function continued to improve until August 1946, when the neurological status became stationary.

The patient was admitted to the Kennedy Veterans Administration Hospital in November 1946. At that time he complained of severe burning pain in both feet. On Feb. 24, 1947 a lumbar sympathectomy was performed on the right side, with removal of the first, second and third ganglia. While there was some improvement in the burning pain after sympathectomy, there developed severe, lancinating pain in both legs, requiring narcotics for relief. In October 1947 a secondary laminectomy, including the twelfth throracic and the first and second lumbar vertebrae, was performed in an attempt to accomplish a lysis of the caudal roots. A thick scar was encountered consisting of greatly degenerated, intertwined roots, bound down by thickened arachnoid. It was technically impossible to free the individual nerve roots fully; however, the cauda equina was sufficiently decompressed that the patient's pain was decreased for approximately three months. In February 1948 severe and intractable root pain recurred, involving chiefly the right leg. The patient became an introvert and antisocial and required constant use of narcotics.

Examination prior to spinothalamic tractotomy showed a status within the limits of normal except for the lower extremities. The patient had an automatic bladder. The bowel was controlled by enemas. All muscles of the lower extremities showed a moderate degree of atrophy. There was a slight degree of voluntary motion of the anterior tibialis and gastrocnemius muscles on the left. Flexion of the left knee was almost normal, but there was no power of extension. The same condition was present in the right leg except for more marked diminution of flexor power in the knee. Sensory examination revealed anesthesia and analgesia below the upper level of the third lumbar dermatome.

On July 23, 1948 a bilateral section of the lateral spinothalamic tract was performed at the level of the first and second thoracic root, resulting in a level of analgesia at the fourth thoracic dermatome on the left and the fifth thoracic dermatome on the right. In order that bladder tone should be maintained, the patient was placed on tidal drainage for the immediate postoperative period. Tidal drainage was discontinued fourteen days after operation, and the patient has since had an automatically functioning bladder, without residual urine. There was no decrease in motor power. The patient was fully relieved of all pain and repeatedly stated that he wished he had had this particular operation sooner. His personality changed almost dramatically. He took an interest in his friends and his family and rapidly made plans for leaving the hospital. He was last seen in September 1949, when he reentered the hospital for a brief checkup. He appeared happy and grateful for what had been done for him. Persistent interrogation revealed the fact that he then experienced no pain of any type.

COMMENT

Most of our patients were treated according to the technic pointed out by Freeman and Heimburger [4] and described in detail by Kahn and Peet.[8] The latter implied that some of the poor results reported in the literature may have been due to the incision being placed too far anterior to the dentate ligament, so that a portion of the sacral segment was

missed. Another source of unsatisfactory results may be associated with obliquity of the incision. It is considered important to perform the tractotomy at a right angle to the long axis of the spinal cord, as can easily be accomplished after adequate rotation of the cord (Kahn and Peet [8]).

Our experience suggests that the tractotomy must be performed bilaterally, even though the patient's pain may be confined to one extremity only. Results of unilateral chordotomy are usually poor because of the spread of pain in the spinal cord [9] and the masking effect which a severe pain exerts on a lesser pain.

Usually spinothalamic tractotomy abolishes orgasm.[10] None of the patients in this series had retained sexual function prior to tractotomy, but our experience with chordotomy in nonparaplegic patients bears out Hyndman and Wolkin's findings.[10]

Scott and Wycis [11] reported temporary bladder dysfunction in 18 per cent and permanent bladder dysfunction in 12 per cent of their cases after chordotomy. While we have seen temporary bladder dysfunction in some of our patients, most of them had satisfactory bladder function after operation and were able to void, without residual urine. In order to maintain bladder tone, we routinely employ Munro's tidal drainage during the immediate postoperative period. The series of cases presented in this paper includes only those of injury of the cauda equina and no conclusions as to the effect of chordotomy on the bladder in nonparaplegic patients can be drawn from this study. Inasmuch as transection of the cauda equina produces bladder automaticity, one would not expect an alteration of the bladder status subsequent to chordotomy.[12]

Three of our patients at first stated they were not relieved of their pain (J. W., R. M. and H. C.). Their behavior and cheerful manner tended to contradict these statements. Finally, these three patients admitted they had been relieved of most of the pain. Two of the patients (R. M. and H. C.) were disciplinary problems and received disciplinary discharges from the hospital because of improper conduct at the time of

9. Ray, B. S., and Wolff, H.: Studies on Pain: "Spread of Pain"; Evidence on Site of Spread Within Neuraxis of Effects of Painful Stimulation, Arch. Neurol. & Psychiat. **53**:257-261 (April) 1945.

10. Hyndman, O. R., and Wolkin, J.: Anterior Chordotomy: Further Observations on Physiologic Results and Optimum Manner of Performance, Arch. Neurol. & Psychiat. **50**:129-148 (Aug.) 1943.

11. Scott, M., and Wycis, H. T.: Survey of the Value of Neurosurgical Treatment for the Relief of Intractable Pain, Am. J. Surg. **77**:718-736 (June) 1949.

12. Meirowsky, A. M.; Scheibert, C. D., and Hinchey, T. R.: Studies on the Sacral Reflex Arc in Paraplegia: I. Response of the Bladder to Surgical Elimination of Sacral Nerve Impulses by Rhibotomy, J. Neurosurg. **7**:33-38 (Jan.) 1950.

an automobile accident on a public thoroughfare. It was believed that their complaint of pain might have been an attempt on their part to forestall the disciplinary discharge.

In view of the uniformly good results with lateral spinothalamic tractotomy for the relief of pain due to injury to the cauda equina, we do not feel that such an operative measure as prefrontal lobotomy or topectomy is justifiable in these cases. These procedures are more radical than tractotomy and, because of possible subsequent personality changes, may jeopardize rehabilitation. Since no deaths appear in the series reported, lateral spinothalamic tractotomy seems, at present, to be a safe method in the treatment of pain subsequent to trauma of the cauda equina.

SUMMARY AND CONCLUSIONS

Eleven cases of intractable pain due to injury of the cauda equina are reported. All patients were significantly relieved of pain by bilateral section of the spinothalamic tract. The study suggests that lateral spinothalamic tractotomy may be the treatment of choice in cases of intractable pain due to injury of the cauda equina. Spinothalamic tractotomy is indicated whenever the pain is of such severity that interference with proper rehabilitation is threatened.

IRRITATING EFFECT OF IODIZED VEGETABLE OILS ON THE BRAIN AND SPINAL CORD WHEN DIVIDED INTO SMALL PARTICLES

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CERTAIN observations made on the unfavorable reaction to emulsions of iodized vegetable oils in the subarachnoid space of animals appear to be of fundamental importance to the neurologist and the neurosurgeon and are the basis of this report.

Some years ago, in a search for a limpid or an absorbable contrast medium for use in roentgenography of the fluid-bearing spaces of the spine and cranial cavity, it occurred to me that an emulsion of one of the commonly used iodized vegetable oils might serve the purpose, since these oils had been proved, by numerous clinical tests over many years, to be relatively free from irritating properties. Frazier and Glaser [1] had apparently already thought along the same line, since in 1928 they suggested the diagnostic use of iodized oil emulsions:

> Another thought occurred to us: If an emulsion of the oil [iodized rapeseed oil] can be prepared which will diffuse rapidly with spinal fluid, such an emulsion, introduced into the ventricles, would be ideal for ventriculography.

While they carried out certain experiments with iodized rapeseed oil emulsion, apparently none was satisfactory because of its irritating property.

EMULSIFIED MATERIALS

Emulsions were prepared from the three standard vegetable oils in common use: iodized oil U. S. P. (lipiodol®; an iodized poppyseed oil), chloriodized oil (iodochloral®; an iodized peanut oil) and iodized corn oil (my own preparation). It was hoped that the emulsion might be absorbed from the subarachnoid space if the particles were small enough—at least that it could be readily withdrawn through a spinal puncture needle when the diagnostic visualization had been completed. Emulsions of these three oils were made, much after the method of Frazer

Presented before the Philadelphia Neurological Society, April 25, 1947.

An abstract of this paper, with discussion, was published in a previous issue of the ARCHIVES (Irritating Effect of Iodized Vegetable Oils on the Brain and Spinal Cord, Arch. Neurol. & Psychiat. **62**:523 [Oct.] 1948).

1. Frazier, C. H., and Glaser, M. A.: Iodized Rape-Seed Oil (Campiodol) for Cerebrospinal Visualization, J. A. M. A. **91**:1609 (Nov. 24) 1928.

and Walsh,[2] by passing a mixture of 50 cc. of iodized oil, 50 cc. of isotonic sodium chloride solution and 5 Gm. of powdered acacia (the dispersing agent) through a high pressure emulsifier especially constructed for me for this purpose (fig. 1). It was possible by this method to produce an emulsion which was stable and which did not break down on being autoclaved. Most of the particles of oil measured less than 12 microns in diameter and thus might readily pass through the channels of exit from the subarachnoid space. There was no sign of free iodine in the completed emulsified materials. The final emulsion before injection was adjusted to a p_H equal to that of spinal fluid.

Acacia was used as the emulsifying agent after it was determined that it had no ill effect on the tissues of the brain and spinal cord of dogs even in as high as a 6 per cent solution. Later, human and dog blood serums were used as the emulsifying materials, with no change in the experimental results. Incidentally, blood

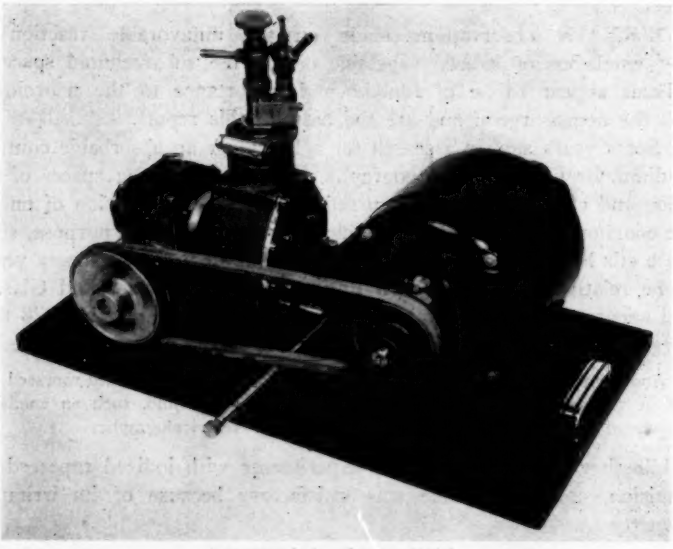

Fig. 1.—Pressure emulsifier used for preparing highly dispersed iodized oil emulsions.

serum was found to be an excellent dispersion agent. Controls were run by injecting iodized oil U. S. P., chloriodized oil and iodized corn oil in the same fashion as were the emulsions of these oils. Even in large quantities these oils produced no irritation. Dogs were used as the experimental animals.

EXPERIMENTAL PROCEDURE AND RESULTS

Approximately 0.5 cc. of iodized oil emulsion for each 10 pounds (4.5 Kg.) of body weight was injected into the spinal subarachnoid

2. Frazer, A. C., and Walsh, V. G.: An Apparatus for the Production of Finely Dispersed Emulsions, and the Rate of Digestion of Fat by Lipase in Relation to the Surface Area, J. Physiol. **78**:467, 1933.

space, cisterna magna or ventricle of dogs, using each of the vegetable oils mentioned. The general result of the injection of the emulsion into each of these locations varied little except that the reaction was greatest near the site where the material was deposited. All the dogs became ill immediately after the injection, and most of them survived longer than 24 hours. Their illness increased, and most of them died within two weeks; those that lived for this period were so sick as to require being killed. The animals with injections in the spinal subarachnoid space frequently became paraplegic, but no part of the subarachnoid space escaped the devastating effect of the emulsion. Necropsy disclosed that there had been definite attempts to encapsulate pockets of the emulsion, and in the long-standing preparation the adhesions at the site of injections were extensive. The tissues in the spinal canal and at the base of the brain were matted together with inflammatory granulations and exudate. Abscess formation or extensive purulent exudate was not a feature of the reaction.

No rational explanation can be given for this reaction to the small particles of iodized oil. Each of the ingredients of the emulsion was adequately tested without any irritation being noted. Since human and dog serums used as the emulsifying agents gave the same results as acacia, it is assumed that the phenomenon must be a physical one, an irritation from the tiny particles of the oil. This poses the question of irritation from the fine particles left in the patient's spinal subarachnoid space when iodized oil has been injected for diagnostic purposes. The irritating effect of extremely small particles of iodized oil also suggests that any colloidal suspension may have a similar effect when injected subthecally.

EFFECT OF ETHYL IODOPHENYLUNDECYLATE (PANTOPAQUE®) EMULSION IN THE CISTERNA MAGNA

Since the first of these experiments was completed, ethyl iodophenylundecylate has come into common use for spinal myelography and has justly displaced the other iodized oils, air and colloidal thorium dioxide (thorotrast®) as a contrast medium in the procedure. It is beyond doubt the most valuable material yet devised for this purpose, for the reason that it can be (and should be) entirely removed at the completion of the myelographic study.

In order to bring this study up to date, an emulsion of ethyl iodophenylundecylate was recently prepared in precisely the same manner as that described for the poppyseed, peanut and corn oils, except that the emulsion was made in a colloid mill. When it was injected into the cisterna magna of dogs in the same quantities as those used of the other oil emulsions, there was immediate death of the animal within 10 minutes. This effect, demonstrated in five dogs, indicates that an emulsion of

ethyl iodophenylundecylate is extremely toxic—even much more irritating than similar emulsions of the iodized oils previously used.

Inflammatory reactions in the spinal subarachnoid space following the injection of various iodized oils have been reported by many clinicians. It is seldom, however, that serious complications have developed after their use. Strangely, many of the unfavorable reactions have followed the attempted removal of the oil by opening the dura at the time of surgical exploration at the cauda equina or after the removal of a

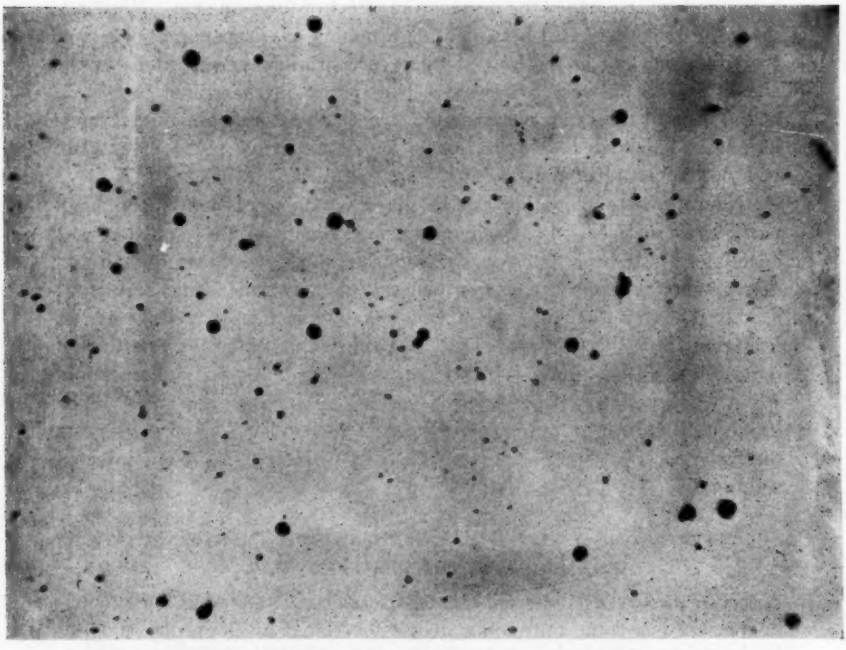

Fig. 2.—Dispersed particles of iodized oil (ethyl iodophenylundecylate; pantopaque®) three days after routine myelographic examination. The number shown here probably cause little or no harm. But if such colloidal particles are numerous, they can cause great irritation and incurable intrathecal adhesions.

tumor of the thoracic or lumbar region of the cord. Marcovich, Walker and Jessico,[3] in their careful study of this problem, stated:

> . . . . however, after the injection of iodized oil the dura mater is opened at operation, the oil commonly becomes rapidly encysted by proliferation of the arachnoid membrane. Pia-arachnoid reactions would therefore seem to be less likely if the dura is not opened.

3. Marcovich, A. W.; Walker, A. E., and Jessico, O. M.: The Immediate and Late Effects of the Intrathecal Injection of Iodized Oil, J. A. M. A. **116**:2247 (May 17) 1941.

In the early days of intervertebral disk surgery it was not uncommon to find a matting, fibrous constriction of the cauda equina on reopening the dural canal. This state was undoubtedly caused by a combination of irritation from the dispersed iodized oil and the extensive transdural surgical approach of that time. Dispersion of the oil was encouraged by the attempt to mop out the oil in a bloody spinal fluid, which served as an ideal emulsifying medium. Extensive adhesions are no longer found when the ethyl iodophenylundecylate, now in common use, is completely removed prior to operation.

In view of the experiments with iodized oil emulsions described here, it would seem logical to assume that it is the tiny dispersed particles of the oil that cause the irritation. Blood serum is an effective emulsifying agent; therefore it should be reasoned that a mixture of iodized oil with bloody spinal fluid may result in dispersing the oil as tiny irritating droplets.

The lesson to be learned from this study is that iodized oils should be instilled into the subarachnoid space with due regard to their potential irritating property and, to prevent ill effects, they should be removed completely whenever possible, either before or immediately after the surgical procedure.

Jefferson Hospital (7).

INTERRUPTION OF BULBOCAPNINE CATALEPSY IN RATS BY ENVIRONMENTAL STRESS

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IT IS WELL known that several drugs produce symptoms which closely resemble common clinical syndromes seen in certain psychiatric patients. Since 1910 considerable attention has been focused on the effects of one of these drugs, bulbocapnine, which experimentally produces in animals practically all of the motor manifestations seen in human catatonia. In a long series of experiments extending over many years, deJong and collaborators exhaustively studied the relation of bulbocapnine catalepsy to human catatonia.[1] They concluded that the phenomena are very similar and that bulbocapnine and other catalepsy-producing drugs have a common denominator in that all produce a derangement in the metabolism of the central nervous system which results in the catatonia. The work of deJong has been critically treated by Ferraro and Barrera[2]; and their monograph, together with deJong's book, presents a comprehensive review of the subject of bulbocapnine catalepsy.

Several studies have been made in this laboratory to determine by what means the catalepsy of bulbocapnine can be abolished, with the hope that such information might be of therapeutic importance to man.

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* Henry Strong Denison Scholar for 1949-1950.

From the Psychobiological Laboratory, Phipps Psychiatric Clinic, and the Department of Physiology, The Johns Hopkins University School of Medicine.

This study was carried out under a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

1. DeJong, H. H.: Experimental Catatonia: A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology, Baltimore, Williams & Wilkins Company, 1945, p. 225.

2. Ferraro, A., and Barrera, S. E.: Experimental Catalepsy, New York State Hospitals Press, 1932, p. 119.

Richter and Paterson [3] devised a method for measuring objectively the degree of catalepsy induced in monkeys used in several of these studies. The presence of the grasp reflex has long been recognized as one of the characteristics of bulbocapnine catalepsy. According to the method of Richter, the strength of the reflex is determined by measuring the length of time a monkey will hang from a horizontal bar after one hand of the monkey has been placed on it.

Using this objective test for catalepsy, Paterson and Richter [4] (1933) showed that scopolamine produced a marked prolongation of the effects of bulbocapnine. They found also that carbon dioxide in low concentrations increased the duration of the catalepsy but that the same compound when inhaled in high concentrations caused a transient disappearance of the syndrome. Loevenhart, Lorenz and Waters [5] had reported four years previously that in cases of human catatonia high concentrations of carbon dioxide brought about temporary disappearance of the stupor. Later, in 1933, Buchman and Richter [6] found that experimental catalepsy produced in monkeys by bulbocapnine could be terminated by the injection of cocaine. They reported that the animals behaved normally almost at once and did not return to the stuporous condition. They cited the work of Berger,[7] Fleck [8] and others who used cocaine in cases of human catatonia to produce a brief interruption of the catatonic state.

Since the work of Buchman and Richter,[6] little attention has been given in this laboratory to studies of bulbocapnine catalepsy. Levine and Wolff [9] used the drug to immobilize animals for surgical procedure with local anesthesia. Recently, we have used it similarly in monkeys, cats and rats during studies of vision and hearing by means of conditioned galvanic skin responses, reported by one of us (H. N. W.).[10] In

3. Richter, C. P., and Paterson, A. S.: Bulbocapnine Catalepsy and the Grasp Reflex, J. Pharmacol. & Exper. Therap. **43**:677, 1931.

4. Paterson, A. S., and Richter, C. P.: Action of Scopolamine and Carbon Dioxide on Catalepsy Produced by Bulbocapnine, Arch. Neurol. & Psychiat. **29**:231 (Feb.) 1933.

5. Loevenhart, A. S.; Lorenz, W. F., and Waters, R. M.: Cerebral Stimulation, J. A. M. A. **92**:880 (March 16) 1929.

6. Buchman, E. F., and Richter, C. P.: Abolition of Bulbocapnine Catatonia by Cocaine, Arch. Neurol & Psychiat. **29**:479 (March) 1933.

7. Berger, H.: Untersuchungen über den Zellgehalt der menschlichen Grosshirnrinde, Ztschr. f. d. ges. Neurol. u. Psychiat. **69**:46, 1921.

8. Fleck, U.: Über Cocainwirkung bei Stuporösen, Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:84, 1924.

9. Levine, M., and Wolff, H. G.: Cerebral Circulation: Afferent Impulses from Blood Vessels of the Pia, Arch. Neurol. & Psychiat. **28**:140 (July) 1932.

10. Wagner, H. N., Jr.: Objective Testing of Vision with the Use of the Galvanic Skin Response, Arch. Ophth. **43**:529 (March) 1950.

the course of using bulbocapnine merely to immobilize the animals, we made observations which led us to perform the experiments presented in this report.

Whereas inhalation of high concentrations of carbon dioxide or the injection of cocaine temporarily abolishes the stupors in catatonia and in bulbocapnine catalepsy by its effect on the internal environment of the animal, we have found that various factors in the external environment can likewise cause disappearance of the catalepsy induced by bulbocapnine.

PROCEDURE

Sixteen wild Norway rats recently captured on the streets of Baltimore and 32 domesticated rats from the Richter colony were used as experimental animals. They were divided into six groups of eight animals each. After catalepsy had been induced, two groups were subjected to intensive auditory stimulation; two groups were studied in a "fighting" chamber, and, finally, two groups were placed in a tank containing deep water.

RESULTS

Audiogenic Seizures.—Group A consisted of 4 male and 4 female adult domesticated rats that were selected for susceptibility to audiogenic seizures. These animals had been stimulated with a 4 inch (10 cm.) electric bell on six or more occasions prior to this experiment in trials carried out intermittently over a period of several weeks. When subjected to this auditory stimulation, the rats always had had seizures consisting of preliminary trembling and markedly increased respiration, then violent and undirected running, followed by a convulsive phase, characterized by tonic and clonic muscular spasms over the entire body.

Ten minutes after the intraperitoneal injection of 45 mg. of bulbocapnine per kilogram of body weight, all eight rats displayed a typical cataleptic stupor. The animals were then placed one at a time in the auditory chamber [11] with all four legs extended laterally, so that the animal rested on its chest and abdomen.

After the animal had remained in this position two or three minutes without movement, the bell was turned on. When the stimulus began, the animal remained in its awkward position at the center of the chamber directly under the bell. None showed signs of excitement which a normal rat displays in the presence of a loud noise (i. e., increased respiration, attempts to escape or aimless darting about). After a latent period of from 20 to 60 seconds of continuous stimulation, during which time the animal remained absolutely motionless, each rat pulled its feet back underneath its body, stood for a few seconds

11. This chamber consisted of a circular metal drum 30 inches (76 cm.) in diameter and 4 feet (120 cm.) in height. A 4 inch bell operated by three no. 6 dry cells was suspended by a cord in the center of the chamber 12 inches (30 cm.) from the floor. The chamber was covered with plate glass to permit observation.

and then began violent running about the chamber. The running phase lasted from one to three minutes and was followed by a convulsive stage. The stimulus was stopped when the convulsion began.

Immediately after the termination of the seizures, the rats were again tested for catalepsy. In every case they displayed symptoms identical with those in evidence immediately preceding the stimulation, such symptoms lasting about an hour. All these rats reverted to catalepsy of long duration immediately after a sound-induced convulsion. It is known that rats convulsed without bulbocapnine also show some signs of catalepsy, but in these animals the catalepsy is of short duration and of a different character.

To demonstrate further that the seizure was "breaking through" the bulbocapnine catalepsy and was not a direct effect of the drug, group B, consisting of eight domesticated rats previously shown by at least six trials to be nonsusceptible to sound-induced seizures, was studied. These rats were given an injection of the same dose of bulbocapnine as were the animals in group A. After demonstration of catalepsy, they were stimulated in the same manner as those in the previous group. None showed any signs of running seizures or convulsions; rather, they remained in their molded position throughout the two minutes of auditory stimulation and showed no decrease in cataleptic symptoms in the period thereafter.

Fighting Chamber.—Group C consisted of eight recently trapped wild Norway rats, ranging in weight from 175 to 425 Gm. There was an equal number of males and females.

Each rat was given an injection of 50 mg. of bulbocapnine per kilogram of body weight. After 10 minutes they were tested for catalepsy. It was found that they could be "molded" into atypical positions in the same way as domesticated rats, that they could be handled without fear of attack and that the doors of their cages could be left open indefinitely without the rats attempting to move or escape.

When catalepsy was in evidence, the rats were placed in pairs in a "fighting" chamber,[12] which is used in this laboratory as an objective method of testing aggressive behavior in rats.[13] Whereas most domestic rats when shocked make no attempt to attack each other, wild rats show very different behavior. The initial shock in most cases causes

12. The chamber consists of a box 12 by 12 by 18 inches (30 by 30 by 46 cm.) with a glass front to permit observation. The floor is a metal grill, alternate rods of which are wired to the terminals of an induction coil. A switch in the circuit permits the operator to deliver current to the grill at his discretion, thus giving them a shock.

13. Richter, C. P.: Use of the Wild Norway Rat for Psychiatric Research, J. Nerv. & Ment. Dis. **110**:379, 1949.

them to start fighting; and only an occasional shock suffices to maintain a continuous battle, during which they often inflict grave injuries on each other.

When the cataleptic wild rats were shocked, they all fought immediately and viciously, just as in the normal state. As long as intermittent shocks were delivered, no evidence of catalepsy was seen, and they continued their vicious fighting.

On cessation of the shocking, the rats returned to their motionless poses; however, very slight disturbances, such as tapping the glass front with a pencil, would start them fighting again. No longer could the animals be handled directly, and if the cage doors were opened they immediately tried to escape. Thus, although they showed some evidence of catalepsy, as evidenced by their motionless poses after the shocking procedure, they were, nevertheless, much less cataleptic than before.

Group D was made up of eight domesticated rats. These rats, in pairs, were subjected to 24 shocks (delivered at five second intervals), in a fighting chamber. No signs of aggressive behavior appeared; however, the rats made many wild attempts to escape, leaping and jumping around when shocked.

The animals were removed from the chamber, given injections of bulbocapnine and tested for catalepsy at the end of 10 minutes. After the syndrome was in evidence, they were again paired off and shocked. No aggressive behavior occurred; nevertheless, the "break through" was again in evidence. The rats leaped about when shocked, vocalizing often. They were not as active, however, as in the precataleptic trials. When the shocks were discontinued, they were again cataleptic, but noticeably less so than in the preshock demonstration.

Swimming Behavior.—Groups E and F consisted of 16 rats—eight adult domesticated rats and eight recently captured adult wild Norway rats. Each rat received an injection of bulbocapnine in the amount of 50 mg. per kilogram of body weight, and after 10 minutes catalepsy was demonstrated.

Then the rats were placed, one at a time, in a tank about 10 feet in diameter containing about 2 feet of water. Two of the rats (both wild) swam about in a normal manner immediately. The other 14 rats floated on the water before beginning to swim; however, within 20 seconds all the rats swam, and, once the swimming movements began, they swam in a normal manner. After 10 minutes of continuous swimming, the rats were removed from the water and were immediately tested for catalepsy. All showed positive signs; all could be molded into atypical poses; none shook themselves as normal rats do after coming out of the water, and the wild rats could be handled with impunity.

Previous studies by one of us (H. N. W.)[10] have shown that monkeys, cats and rats remain alert to sensory stimuli although in the cata-

leptic state, as a result of injection of bulbocapnine. Intact vision and hearing in particular were demonstrated by conditioned galvanic skin responses. The animals thus are in rapport with their environment but do not move. In this respect the animals under bulbocapnine resemble human catatonic patients, in whom rapport with their environment has frequently been demonstrated.

In this report we describe the observation that various stressful environmental factors result in a transient, but complete, disappearance of the cataleptic state. During the periods of stress, at least two of which may be considered life-threatening situations, the rats behaved in a maner indistinguishable from normal animals in the same circumstances.

These observations add to the previously accumulated evidence that experimental bulbocapnine catalepsy reproduces more than just the motor component of catatonia, i. e., the loss of motor initiative and the maintenance of passively impressed postures. The "break through" of catalepsy in the presence of environmental stress is also frequently seen in catatonic patients. For example, forced inhalation of high concentrations of carbon dioxide, which causes a disappearance of the cataleptic symptoms,[5] may be considered a life-threatening situation. In addition, sudden motor outbursts during which the patient suddenly becomes aggressive and violent are common occurrences in cases of human catatonia.

SUMMARY

Three technics which result in the temporary interruption of catalepsy induced in rats with bulbocapnine are described: (1) intensive auditory stimulation, (2) electric shocking in a situation which results in fighting and (3) immersion in deep water. These methods have in common that they all constitute some form of stress in the external environment.

The observations, together with previous findings, indicate that bulbocapnine catalepsy not only reproduces the motor component of human catatonia but also disappears under similar environmental conditions.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

HISTOLOGIC CHANGES IN SENSORY NERVES OF THE SKIN IN HERPES ZOSTER. MICHAEL H. EBERT, Arch. Dermat. & Syph. **60**:641 (Nov.) 1949.

Ebert attempted to demonstrate histologic changes in the skin in association with herpes zoster. He studied biopsy specimens in 15 patients, using Prieto's modification of the Cajal silver impregnation method. The patients varied in age from 17 to 78 years. Only 12 specimens were adequate for study.

Many fewer nerve fibers were found in the middle and deeper layers of the corium when the vesical site was removed 14 or more days after the eruption. Not all the nerve bundles were affected, and not all the fibers in a single bundle were involved. Degeneration occurs not only at the site of the lesion but in normal skin near the lesions. The loss of fibers in the skin is irreversible.

ALPERS, Philadelphia.

Physiology and Biochemistry

EFFECTS OF INTRAVENOUSLY ADMINISTERED AMINOPHYLLINE ON CEREBRAL CIRCULATION AND METABOLISM IN MAN. R. L. WECHSLER, L. M. KLEISS and S. S. KETY, J. Clin. Investigation **29**:28 (Jan.) 1950.

The effects of administration of clinically therapeutic doses of aminophylline were studied on the blood gases, the p_H of the blood, cerebral blood flow, cerebral oxygen consumption and cerebrovascular resistance in 10 hospitalized patients without obvious cerebral depression. The most striking result was a statistically significant decrease in cerebral blood flow. An expected increase in respiration occurred.

The authors believe it is probable that aminophylline constricts the cerebral vessels and thus causes a decrease in cerebral blood flow. With the decrease in cerebral flow, the carbon dioxide tension of the brain would be expected to increase. Since increased carbon dioxide tension is a known respiratory stimulant, they suggest that the cause of the hyperventilation resides in the diminished cerebral blood flow. This hyperventilation diminishes the carbon dioxide blood tension of arterial blood and results in a decrease in the tension of the brain and of the internal jugular venous blood to its previous level. With the decrease in cerebral flow achieved, however, and a constant over-all oxygen consumption, the oxygen content of the internal jugular venous blood falls. Since the oxygen content of the internal jugular venous blood is a reflection of the oxygen content of the brain, aminophylline produces anoxia of cerebral tissue.

Four of the patients reacted to the drug with pronounced anxiety associated with disturbing symptoms and an increase in cerebral oxygen consumption.

ALPERS, Philadelphia.

METABOLISM OF BRAIN TISSUE SLICES AND SUSPENSIONS IN VARIOUS MAMMALS. K. A. C. ELLIOTT, J. Neurophysiol. **11**:473, 1948.

Elliott studied the metabolic rates of excised brain tissue from a series of animal types. Mice, rats, guinea pigs, rabbits, cats, dogs and monkeys were

employed. Fresh, recently killed beef brains were included. Elliott found that the rate of oxygen uptake of slices of cerebral cortex is roughly inversely proportional to the tenth root of the average body weight of the species. The respiration rate varies widely in different individuals within a species, and there is variation in rate between various portions of the brain. Aerobic glycolysis actively occurs in brain tissue slices but not in suspensions. The relative anaerobic glycolytic activity increases with increasing size of the animal.

FORSTER, Philadelphia.

RELATIONSHIPS BETWEEN CEREBRAL AND CEREBELLAR CORTICES IN CAT. J. L. HAMPSON, J. Neurophysiol. **12**:37, 1949.

Hampson studied the relations between the cerebral and the cerebellar cortex in the cat. He stimulated electrically specific functional areas of the cerebral cortex and recorded alterations in electrical activity from the cerebellar cortex. He found that stimulation of somatic area I evoked responses in the contralateral anterior lobe and lobulus simplex, whereas stimulation of somatic area II evoked responses from the contralateral paramedian lobule. The auditory areas of the cerebral cortex projected to the folium vermis and tuber vermis in an overlapping manner. The autonomic center for the eyes, situated on the medial aspect of the cerebral hemisphere, is represented primarily in the contralateral cerebellar hemisphere, the upper folia of the adjacent paramedian lobule and the lateral arm of the lobulus simplex.

FORSTER, Philadelphia.

ELECTRONARCOSIS: II. INHIBITION OF ELECTRICAL ACTIVITY OF CEREBRAL CORTEX FOLLOWING APPLICATION OF PULSED STIMULUS TO DIENCEPHALON. E. MARTINI, T. GUALTIEROTTI and A. MARZAROTI, J. Neurophysiol. **13**: 1, (Jan.) 1950.

The application of a pulsed current directly to the diencephalon is followed by the appearance of continuous or spindled slow waves (10 to 18 per second) in the motor area of the cerebral cortex. The slow waves are bilateral in phase, but frequently of different amplitude on the two sides. This state may progress to the complete inhibition of electrical activity. Occasionally spikes similar to those obtained from a single nerve or muscle fiber appear at a frequency of 10 to 18 per second. These spikes are probably the expression of the activity of one or more cells which escape inhibition.

In a very limited area of the frontal lobes the effect of the stimulus is to accentuate the slow rhythms. The area which, when stimulated, produces the inhibition of the cerebral cortex is close to the mamillary bodies, next the center controlling the electrical activity of the upper part of the spinal cord.

ALPERS, Philadelphia.

CORTICAL INHIBITION OF GASTRIC MOTILITY. B. P. BABKIN and T. J. SPEAKMAN, J. Neurophysiol. **13**: 55 (Jan.) 1950.

Inhibition of pyloric-antral motility occurs from the "insular-orbital" region and the subgenual portion of the anterior cingulate gyrus. No augmentation of antral motility was produced in this series by stimulation anywhere on the exposed cortex.

A functional relation between the orbital surface and the anterior cingulate gyrus is suggested, and the phylogenetic relation of part of the "orbital surface" of the dog to the island of Reil in man is pointed out.

KELLY, Philadelphia.

EFFECT UPON BLOOD PRESSURE OF ELECTRICAL STIMULATION OF TIPS OF TEMPORAL LOBES IN MAN. W. P. CHAPMAN, K. E. LIVINGSTON and J. L. POPPEN, J. Neurophysiol. **13:** 65 (Jan.) 1950.

Electrical stimulation of the tips of the temporal lobes was found to produce elevation of blood pressure in a patient under thiopental anesthesia. Significant elevations occurred both in the systolic and in the diastolic blood pressure. The responses in the blood pressure were obtained using a current of 10 cycles per second, a pulse duration of 10 milliseconds and a voltage of 5 to 20.

Possible connections between the tips of the temporal lobes and the hypothalamus which might mediate the responses in blood pressure are suggested.

KELLY, Philadelphia.

PATHOPHYSIOLOGIC ASPECTS OF OXYGEN DISTRIBUTION IN THE CORTEX. A. RENARD, Rev. neurol. **80:** 579 (Sept.-Oct.) 1948.

Studies of oxygen distribution in the cortex with the Davies microelectrode, an instrument which measures oxygen potential in vivo, revealed that the lowest oxygen tension exists at a point between a venule and an arteriole and that therefore the veins constitute a source of oxygen for cerebral tissue which may be important in cases of depletion. Studies of the cat cortex in which respiration was artificially maintained during status epilepticus revealed that the oxygen tension of cerebral tissue falls profoundly during a convulsion, independently of vascular oxygen tension, which remains constant in this type of preparation.

LEGAULT, WASHINGTON, D. C.

EFFECT OF ANTIPARKINSONIAN DRUGS ON THE BASAL METABOLISM. J. MAHAUX and K. KOWALEWSKI, Acta neurol. et psychiat. Belg. **49:**441 (June) 1949.

Mahaux and Kowalewski noted the effect of caramiphen hydrochloride (panparnit®; diethylaminoethyl-1-phenylcyclopentane-1-carboxylate hydrochloride) and diethazine hydrochloride (diparcol®; diethylaminoethyl-N-thiodiphenylamine) on the metabolic rate in patients with paralysis agitans. For 17 patients with various extrapyramidal syndromes the basal metabolic rate averaged + 54 per cent, and after the administration of caramiphen it was lowered to + 22 per cent, a reduction of 32 per cent. For 6 patients with senile paralysis agitans the metabolic rate averaged + 39 per cent, and with diethazine hydrochloride it was lowered to + 15.5 per cent, a decrease in 23.5 per cent. For 9 patients with postencephalitic paralysis agitans the metabolic rate was + 49 per cent, and with diethazine it was decreased to + 11 per cent, or a reduction of 38 per cent. The authors state that both these drugs are of value in the practical treatment of the parkinsonian syndromes and that by their sedative effect on the highest centers they decrease the catabolic activities of the body. DEJONG, Ann Arbor, Mich.

Neuropathology

DISSEMINATED NECROTIZING PANARTERITIS (PERIARTERITIS NODOSA). N. W. WINKELMAN and M. T. MOORE, J. Neuropath. & Exper. Neurol. **9:**60 (Jan.) 1950.

Winkelman and Moore report the case of a man aged 63 who had asthma, peripheral neuropathy and eosinophilia in excess of 25 per cent, and who had received sulfonamides and penicillin on two occasions. The antemortem diagnosis

of necrotizing panarteritis was substantiated by biopsy. The presence of an addisonian syndrome was verified by postmortem study of the adrenal glands.

Involvement of the nervous system was clinically recognized as the disease progressed and was confirmed by necropsy studies. Other phases of the classic course of the disease were present, especially the increasing retention of urea and creatinine and the late development of hypertension.

Gross and histologic studies revealed involvement of all systems of the body with the lesions of necrotizing panarteritis, except for the lungs. Histologic study of the brain revealed involvement of the smaller arteries in the meninges, choroid plexus, cortex and subcortex.

Infarctions secondary to either rapid or slowly thrombosed vessels were present. There were also various stages of healed lesions in the cerebral cortex and subcortex, as well as in the cerebellum. The changes in the vessels were characteristic of necrotizing panarteritis. The large vessels were spared. The meninges showed evidence of both recent and old hemorrhage and mild inflammatory invasion.

ALPERS, Philadelphia.

AMYLOID DEGENERATION OF THE HUMAN BRAIN FOLLOWING X-RAY THERAPY. K. LOWENBERG-SCHARENBERG and R. C. BASSETT, J. Neuropath. & Exper. Neurol. **9**:93 (Jan.) 1950.

Lowenberg-Scharenberg and Bassett report two cases of degeneration of a normal human brain following an overdose of roentgen rays. The dominant histologic feature in these cases and in those recorded in the literature was the formation of an amorphous substance in areas of the brain which were exposed to the roentgen rays.

In order to clarify the histogenesis of the amorphous tissue in the brain, the authors compared it with amyloid of the spleen, using the silver carbonate technics of brain histology. It was found that the pattern was basically similar in the two organs: The degeneration was the result of a local response of the tissue, involving cells and fibers. The embryonic origin of the tissue determines the type of elements which react and give rise to "amyloid." Consequently, the amorphous tissue in the brain is predominantly of ectodermal origin, and the reacting cell is the astrocyte. In the spleen it is of mesodermal origin, and the reacting elements are connective tissue fibers and the reticuloendothelial system. Regardless of origin, it is always the supporting tissue which responds, and not the parenchyma. The cycle of histologic events is characterized by proliferation, swelling and hypertrophy of cells and fibers and terminates with the transformation of the reacting cells and structures into an amorphous substance.

ALPERS, Philadelphia.

EPENDYMOBLASTOMA ACCOMPANYING SYRINGOMYELIA. T. DELEHOCZKY, Acta neurol. et psychiat. Belg. **49**:1 (Jan.) 1949.

DeLehoczky reports the case of a man aged 31 in whom there developed segmental sensory changes in the forearms, weakness of the neck, weakness of the forearms and, finally, progressive paralysis, sensory dissociation, total anesthesia and massive paraplegia below the fourth cervical segment. Spinal puncture revealed a complete spinal subarachnoid block. The patient was operated on but died of bronchopneumonia five days later. Pathologic examination revealed a large intramedullary ependymoblastoma, in combination with which there was cavity formation of the type associated with syringomyelia and syringobulbia. The author expresses the opinion that the neoplasm had its origin in the ependyma of the central canal.

DEJONG, Anr Arbor, Mich.

Meninges and Blood Vessels

ESCHERICHIA COLI MENINGITIS TREATED SUCCESSFULLY WITH STREPTOMYCIN S. VERAS and A. MYSTAKIDIS, Am. J. Dis. Child. **79**:115 (Jan.) 1950.

Meningitis due to Escherichia coli is unusual and is observed particularly in newborn children. It is also reported as occurring during infancy subsequent to gastric disturbances. The spinal fluid is usually purulent. The mortality rate in reported cases is high.

The authors report the case of a boy aged 2½ years who was admitted with symptoms of meningitis. A spinal puncture yielded thick, purulent fluid. Penicillin was administered without improvement. Sulfathiazole, 4 Gm. per twenty-four hours, was administered orally for two days without improvement or with aggravation of the patient's state.

Since Esch. coli was identified on culture from the spinal fluid, streptomycin was given intrathecally and intramuscularly, the total daily dose being 900,000 units. Improvement was shown from the third day of treatment on. The duration of treatment with streptomycin was eighteen days, and the total amount of the drug given was 16 Gm. It is noted that the daily amount of streptomycin given this child was greater than that usually employed by the authors for patients with tuberculous meningitis. It was felt that the duration of treatment for Esch. coli meningitis usually is not long and that the total amount of streptomycin used would not exceed the patient's tolerance.

Four weeks after admission a suboccipital puncture showed the fluid to be clear. The culture was negative for the organisms. The child left the hospital two days later in good general health.

ALPERS, Philadelphia.

Diseases of the Brain

MASKED MUMPS ENCEPHALITIS COMPLICATED BY HEMIPLEGIA. H. BLOCH, D. HIRSCHL, R. TURIN and B. ZALEZNAK, Am. J. Dis. Child. **79**:324 (Feb.) 1950.

Mumps encephalitis is not uncommon and is generally considered a mild disease. Death is rare, and recovery is usually rapid and complete.

The case here reported is that of a 16 month old white girl admitted with a temperature of 106 F., unconsciousness and frequent severe convulsions. On her admission the condition was diagnosed as encephalitis. Although there was no enlargement of the salivary glands, a history of contact with mumps suggested the likelihood of masked mumps encephalitis. The complement fixation test of Henle, Henle and Harris identified the mumps virus as the etiologic factor in the encephalitis.

For four days the course of the child's illness was hectic. A flaccid paralysis of the left arm and leg was observed soon after her admission. Convulsions were frequent, and the child was almost constantly comatose. With treatment the fever and convulsions subsided on the fifth day, but the flaccid paralysis of the left arm and leg remained unchanged. Examination three months after onset revealed residual left hemiplegia.

ALPERS, Philadelphia.

RABIES VACCINE ENCEPHALOMYELITIS IN RELATION TO INCIDENCE OF ANIMAL RABIES IN LOS ANGELES. C. F. PAIT and H. E. PEARSON, Am. J. of Pub. Health **39**:875 (July) 1949.

Pait and Pearson state that in Los Angeles city and county approximately 200 rabid dogs are detected annually. There is only 1 human case of rabies per

year, but at least 800 persons are given rabies vaccine. The chance of acquiring rabies from known dog bites in Los Angeles is estimated to vary from 1 : 1,400 to 1 : 2,100. There were 9 cases, 1 fatal, of postvaccinal encephalomyelitis among 5,500 treated persons, an incidence of 1 : 600. The data presented here and elsewhere make it apparent that the incidence of rabies vaccine encephalitis is a real contraindication to its indiscrinminate use. It is likely that the incidence will be reduced when a more completely purified product of brain tissue is produced; at present most vaccines consist of approximately 10 per cent suspensions of rabbit brain. There is evidence that human rabies can be largely prevented by controlling the disease in dogs. There is a large and highly vocal group of dog fanciers who tend to resist all efforts to interfere with the dog population. While such persons may reject programs based on protection of human beings, they can scarcely fail to accept one designed primarily for the protection of dogs.

J. A. M. A.

Encephalitis Following Vaccination Against Pertussis (Editorial). Ann. Int. Med. **32**:343 (Feb.) 1950.

Recent observations indicate that grave injury to the nervous system, with symptoms resembling those described in postvaccinal encephalitis, may follow the administration of pertussis vaccine. The first systematic study was that of Byers and Moll, who reported 15 cases over a period of 10 years. Symptoms appeared after an interval of 20 minutes to 72 hours following the injection. The onset was usually abrupt with high fever, restlessness, irritability or drowsiness, followed quickly by generalized, or occasionally unilateral, convulsions and coma. Usually there were evidences of gross organic cerebral lesions.

All 15 patients reported by Byers and Moll survived the acute illness, which subsided after two to 10 days. Two subsequently died of pneumonia, after periods of progressive deterioration. Of the 13 surviving children, only one showed reasonably satisfactory recovery; in three instances the interval was too short to warrant final conclusions, but in the nine others there were serious, and almost certainly permanent, sequelae, of varying severity.

The pathogenesis of this form of encephalitis is still not established. The close similarity of the encephalitic lesions in this disease and those in the encephalitis accompanying vaccinia, antirabies vaccination, smallpox, chickenpox and measles suggests, although it does not prove, that the same mechanism is involved in the production of them all. The rarity of these attacks strongly suggests that, whatever the mechanisms, they must depend in part on some individual peculiarity or predisposition.

The administration of pertussis vaccine involves a definite, but remote, risk of producing a damaging encephalitis. This encephalitis is comparable in its incidence to the encephalitis following smallpox vaccination; its immediate mortality has been less, but the frequency of severe permanent injury to the brain has been higher. The mortality of pertussis in young children is so high, however, and the protective value of the vaccine so well established that the remote risk of encephalitis should not interfere with the widespread use of the vaccine.

Certain precautionary measures, however, are indicated. All patients should be observed after administration of the vaccine and further doses withheld if severe reactions occur, particularly if there are convulsions or any other reasons to suspect cerebral injury. As a rule, the vaccine should not be given to children

with fever or other evidence of acute illness, to patients with evidence of cerebral damage of other types or to those who have shown manifestations of hypersensitivity.

ALPERS, Philadelphia.

METHYL-PHENYL-ETHYL HYDANTOIN (MESANTOIN) IN THE TREATMENT OF CONVULSIVE DISORDERS. C. MARSH and V. J. MILLER, Bull. Los Angeles Neurol. Soc. **14**:227 (Dec.) 1949.

Mesantoin® (3-methyl-5-phenyl-5-ethyl-hydantoin) was employed in 54 patients with convulsive seizures in whom diphenylhydantoin (dilantin®) or other anticonvulsants were ineffective and/or toxic.

Of the 54 patients studied, the results for 12 were classified as failures: Four of these patients had an increase in symptoms, and it was necessary to stop medication; 8 were not benefited by mesantoin,® and for 6 of these patients the medication was discontinued.

Marsh and Miller believe that mesantoin® is of value in treatment of grand mal and psychomotor epilepsy, reducing the frequency and severity of the attacks. Although of relatively low toxicity, mesantoin® should be employed under close supervision in order that unpleasant side effects may be avoided.

ALPERS, Philadelphia.

COMPLETE PEDUNCULAR SYNDROME: CLINICAL CONSIDERATIONS. B. B. SPOTA and C. A. BARDECI, Rev. Asoc. méd. argent. **63**:66 (Feb. 15-28) 1949.

Spota and Bardeci report a case of a complete peduncular syndrome without anatomic confirmation. A white woman aged 66 suddenly complained of numbness of the left side of the body, followed a few hours later by weakness of the same side. Double vision appeared soon afterward. The complete picture developed over a period of fourteen hours. The blood pressure was 250 systolic and 170 diastolic. Neurologic examination showed paralysis of the right third nerve and left hemiplegia and hemianesthesia, which was more marked in the lower limb. In addition, there was paralysis of upward conjugate and of left lateral conjugate movements of the eyes. There was also pronounced diminution of hearing bilaterally. The authors considered that this syndrome was due to an extensive vascular lesion involving almost the whole right side of the peduncle. The absence of evidence of involvement of the red nuclei is explained by the completeness of the pyramidal tract signs on the left side. The authors considered the syndrome to be due to thrombosis of the posterior cerebral artery near its origin from the basilar artery.

N. SAVITSKY, New York.

SPONTANEOUS INTRACEREBELLAR HEMORRHAGE: SURGICAL TREATMENT. GERMAN HUGO DICKMANN and LEON ZIMMANN, Rev. Asoc. méd. argent. **63**:356 (Aug.) 1949.

A man aged 26 complained of severe headache daily during the month before his admission to the hospital. The bouts of cephalalgia did not respond to analgesic therapy. There was occasional vomiting. Examination on his admission revealed bilateral papilledema, nystagmus on extreme left lateral gaze, paralysis of the right external rectus muscle, mild nuchal stiffness, hypotonia and dysdiadokokinesis on the right side and a bilateral Babinski sign. The serologic reactions of the blood were negative. Ventriculographic studies showed dilatation of the ventricular system. Suboccipital craniotomy showed the right cerebellar hemi-

sphere to be enlarged and displaced to the left. At a depth of 4 cm., dark blood was removed from a cyst in the anterolateral part of the left cerebellar lobe. No tumor was found. There was improvement the day following the operation, and the patient was discharged as recovered in ten days. When reexamined toward the end of March 1949, he was found to be in excellent condition. A spontaneous intracerebellar hemorrhage must be considered, according to the authors, in a patient with acute increase in intracranial pressure and cerebellar signs with or without subarachnoid hemorrhage. N. SAVITSKY, New York.

CONGENITAL FORMATION OF CAVITIES IN THE CEREBRUM: ENCEPHALOGRAPHIC DIAGNOSIS OF PORENCEPHALOUS DEFECTS IN CHILDREN. H. STECH, Wien. med. Wchnschr. **98**:184 (May 1) 1948.

Stech reports a rare case of genuine porencephaly in a girl aged 4½ years. The condition was demonstrated roentgenologically in vivo and established at necropsy. After a presumably normal birth the child was given hospital treatment for debility for three months. She never learned to speak. Because of emaciation and mental deterioration, the child was readmitted to the hospital. She was apathetic and subject to convulsions. Encephalographic study revealed a porencephalous defect in the region of the left frontotemporoparietal triangle, communicating with the lateral ventricle and with the subarachnoid space on the same side. The defect was of Guttmann's porus communicans type. Five days after the encephalographic examination the child became lethargic, and death occurred after repeated convulsions. It is suggested that the porencephaly could have been caused by trauma to the brain during delivery. Encephalography appears to be adequate in demonstrating the lesion in cases of doubtful cerebral disturbances. J. A. M. A.

A CASE OF SPONTANEOUS SUBDURAL HEMATOMA. J. VAN LAERE, Acta neurol. et psychiat. Belg. **49**:38 (Jan.) 1949.

Van Laere reports the case of a man aged 56 who had onset of mental symptoms suggestive of dementia paralytica together with intermittent right-sided headaches. Clinical examination showed anisocoria, with the pupil on the right smaller than the left and normal pupillary reflexes. There were papilledema on the right and weakness of the lower extremity on the left. Roentgenograms of the skull were normal, but ventriculographic studies showed displacement of the anterior horn of the right lateral and third ventricles. Surgical exploration showed a large subdural hematoma in the frontal and parietal regions on the left side. There was no history of trauma, alcoholism, syphilis or blood dyscrasia to explain the cause of this spontaneous hematoma. DEJONG, Ann Arbor, Mich.

BRAIN TUMOR IN PREGNANCY. P. DIVRY and J. BOBON, Acta neurol. et psychiat. Belg. **49**:59 (Feb.) 1949.

The association of cerebral tumor and pregnancy, while rare, imposes difficult problems in diagnosis and treatment. Seventy-one cases have been found in the literature, and the authors report on 3 such instances. In 80 per cent of the cases the pregnancy seemed to have a definite influence on the growth of the neoplasm, and in 20 per cent delivery itself precipitated the symptoms. The diagnosis of brain tumor during pregnancy is made difficult by the fact that the symptoms may resemble those of toxicity of pregnancy. The pathogenesis of the neoplasms is obscure. The rapid progression of these tumors at the time of delivery may

be related to changes in cerebral circulation. The therapeutic approach varies with the individual case. In general, neurosurgical intervention seems indicated at the time of the recognition of the existence of the tumor.

DEJONG, Ann Arbor, Mich.

ALEXIA IN CHILDREN. P. LIESSENS, Acta neurol. et psychiat. Belg. **49**:102 (Feb.) 1949.

Liessens observed 16 children with varying degrees of a disability characterized by difficulty in reading. The children, however, did not have the defect in computation which would place them in the category of congenital alexia. The principal defect was in the ability to organize letters into syllables and syllables into words and in the ability to learn words as visual symbols.

DEJONG, Ann Arbor, Mich.

NEURO-OPHTHALMOLOGIC STUDY OF TWO GENEALOGIES OF HEREDODEGENERATIVE NEURAL AMYOTROPHY. J. FRANCOIS and L. DESCAMPS, Acta neurol et psychiat. Belg. **49**:648 (Sept.) 1949.

Francois and Descamps studied two families with heredodegenerative neural amyotrophy from a neuro-ophthalmologic point of view. One of the families showed a disturbance of the Charcot-Marie-Tooth type, and the other had a disorder which corresponded to the classification of progressive hypertrophic neuritis of Déjerine and Sottas. In both families the authors found frequent pupillary abnormalities with unequal and irregular pupils, disturbance of the light reflex and disorders of the sensory and orbicular reflexes.

DEJONG, Ann Arbor, Mich.

CHORIORETINAL CHANGES IN TWO SISTERS WITH FRIEDREICH'S ATAXIA. W. STADLIN and L. VAN BOGAERT, Acta neurol. et psychiat. Belg. **49**:705 (Sept.) 1949.

Stadlin and van Bogaert observed changes in the retina and choroid in 2 sisters with Friedreich's ataxia. The changes consisted principally of pigmentary degeneration; there was no optic nerve atrophy in either case.

DEJONG, Ann Arbor, Mich.

Treatment, Neurosurgery

ARTERECTOMY IN TREATMENT OF INTRACTABLE PAIN FOLLOWING RECOVERY FROM ACUTE ARTERIAL OCCLUSION. N. E. FREEMAN, F. H. LEEDS and R. E. GARDNER, Am. Heart J. **38**:329 (Sept.) 1949.

Freeman and his associates point out that after recovery from acute occlusion of a major artery to the extremity, even though the circulation is sufficient for tissue nutrition, the patient may have severe rest pain with paresthesias and numbness of the extremity. This pain has been termed ischemic neuritis. Temporary relief may be obtained by blocking the sympathetic nerves to the leg, but sympathectomy is contraindicated. The site of obstruction was visualized by arteriography in 10 patients. Excision of a segment of the thrombosed artery was followed by immediate relief from the pain. There was no significant increase in circulation after this procedure. Arterectomy is of value in the treatment of this type of pain through the interruption of some nervous reflex which originates from the thrombosed artery.

J. A. M. A.

CHEMICAL STRUCTURE OF SUBSTANCES EFFECTIVE IN TREATMENT OF PARKINSONISM. D. S. GAIR and J. DUCEY, Arch. Int. Med. **85:** 284 (Feb.) 1950.

The present study was designed to determine what chemical configuration, present in the formulas of certain antihistamine drugs, may be essential to activity in the palliation of the symptoms of parkinsonism.

Trials of ten antihistamine drugs in a series of 63 cases are reported. The series covered an eight month period of observation, and the study was controlled by the use of physically identical placebos of all the drugs used.

Trimeton® (1-phenyl-1-[2-pyridyl]-3-dimethylaminopropane) and decapryn® (2-[α-(dimethylaminoethyoxy)-α-methylbenzyl] pyridine succinate), not previously reported in this connection, are recorded as being effective in palliation of symptoms in 60 and 51 per cent of trials, respectively. Diphenhydramine (benadryl®), previously reported as successful, was found to be effective in this series in 64 per cent of its trials. Thephorin® (2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene hydrogen tartrate) previously reported as successful, elicited equivocal results with a high incidence of side effects and 28 per cent good results.

Tripelennamine (pyribenzamine®), histadyl® (N, N-dimethyl-N'[2-thenyl]-N'-[2-pyridyl] ethylenediamine hydrochloride) antistine® (2-[N-phenyl-N-benzylamino-methyl] imidazoline hydrochloride) A-446, L-01780 (an isomer of benadryl®) and S-111 (*p*-tolyl-2-pyridyl-β-dimethylaminoethyoxymethane) elicited poor results.

The authors discuss certain similarities in the chemical structures of the effective substances used and in other reported effective medicaments and describe a skeleton formula for an effective substance.

They also note that under optimal medication in patients with parkinsonism there remains a definite residue of obvious disease. ALPERS, Philadelphia.

THYMECTOMY IN THE TREATMENT OF MYASTHENIA GRAVIS. L. M. EATON and C. T. CLAGETT, J. A. M. A. **142:**963 (April 1) 1950.

Three hundred patients with myasthenia gravis were studied; of these, 86 underwent surgical treatment for removal of the thymus, a thymic tumor or both. For purposes of this study, comparison is made of 72 cases of myasthenia gravis in which surgical treatment was employed and 142 control cases in which nonsurgical treatment was used. Favorable results were more frequent among the surgical cases, but further analysis of the two series suggests that factors having to do with selection of cases for surgical therapy account for the superior results. Eaton and Clagett state that their study fails to support the thesis that thymectomy influences beneficially the course of myasthenia gravis.

At present, thymectomy in the treatment of myasthenia gravis is recommended by the authors because of the potentially malignant character of the thymoma, and not because of anticipated improvement in the myasthenia gravis.

ALPERS, Philadelphia.

Diseases of Bones

RESECTION OF THE INTERVERTEBRAL DISK THROUGH THE POSTERIOR APPROACH. S. L. HAAS, Arch. Surg. **50:**1261 (Dec.) 1949.

In dogs intervertebral lumbar disks were removed as thoroughly as possible by posterior approach. Bony bridging between the involved vertebral bodies was roentgenographically demonstrated in young animals after a period of four months, but in no case was the disk completely replaced by bone. In older animals the bony proliferation was slight. Some of the dogs showed increased mobility of the spine at the site of the removed disk. LIST, Grand Rapids, Mich.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY AND THE NEW YORK NEUROLOGICAL SOCIETY

Lewis D. Stevenson, M.D., *President, New York Neurological Society, in the Chair*

Combined Meeting, April 12, 1949

Seizures, Head Injuries and Litigants. Dr. George H. Hyslop, New York.

The records of 750 patients engaged in litigation who had actual or alleged head injuries of varying kinds and degrees of severity were studied.

The problem of the relation of injury to seizures occurred in 65 cases. Thirteen patients had sustained organic and focal damage to the brain, evident within a day or so of the injury. Two of these patients were injured during their first known seizure. The others had their first seizures a few months to two years after the injury. In some instances seizures ceased after a few years. Malingering did not occur in this group of patients.

Fifty-two patients alleged to have had at least concussion reactions, but the actual injury was concussional or less. Analysis of the records of these 52 patients showed the following facts:

1. In 12 patients the alleged head injury did not occur.

2. Twenty-eight, or 54 per cent, misrepresented the actual degree of injury sustained.

3. Eighteen patients were injured in the course of a seizure; 6 of these were injured during their first known seizures.

4. Six patients probably were injured during seizures; 3 of these patients were liars.

5. Seven patients probably had seizures before their injuries. Three of these patients malingered during physical examination, and the other 4 had preinjury disease of a nature making the occurrence of seizures highly probable.

6. Fifteen patients sustained injury not due to a seizure but admitted having had previous attacks. In 3 of these patients the seizure pattern was temporarily aggravated.

7. Five patients with nontraumatic disease that might cause seizures had one or more attacks at varying intervals after their injuries but apparently had had no seizures previously.

8. One patient, aged 33, who apparently had recovered from his concussion, had two petit mal attacks a year later. No cause for these attacks could be found.

Conclusions.—1. The frequency of fraud by patients whose injuries have not caused evident organic damage to the brain requires special care in establishing the facts. One must inquire whether there were seizures prior to injury, whether the injury possibly occurred in the course of a fit, whether a known injury has altered the pattern of previous fits and whether there is any nontraumatic cerebral or other physical disease which may cause fits.

2. From the study of these 750 cases, it would seem that in the healthy person the reaction of the brain to injury limited to a concussion or some less severe effect does not lead to recurring fits at a later date.

3. Post-traumatic epilepsy is an undesirable term. "Traumatic epilepsy" is to be preferred as not being ambiguous and as not giving improper emphasis on the time factor.

DISCUSSION

DR. MICHAEL SCOTT, Philadelphia: It is significant that in Dr. Hyslop's series of 13 patients with proved focal damage of the brain not one attempted fraud, whereas of his series of 52 patients with alleged head trauma with symptoms of concussion, 54 per cent presented malingering or fraud. It is therefore obvious that once litigation enters the picture, particularly if the head injury was minimal, the physician should be on his guard against dishonesty from any quarter. However, it is frequently difficult to distinguish between the justifiable exaggeration of symptoms which an illiterate or ignored patient might show and those presented by the malingerer. In many instances the patient has been out of work for a long period. He has no money; his case drags on for months. How can he impress his counsel and the attending physician with the importance of his case except by some exaggeration? In fact, the patient may even acquire a true post-traumatic anxiety neurosis on that basis alone.

In my experience, the electroencephalogram has been of little value in these debatable cases. One would not indict a person medically, legally and socially as epileptic solely on the basis of significant abnormalities in the electroencephalogram and without a definite history of convulsions—petit mal, grand mal or psychogenic. Similarly, a normal electroencephalogram would not prove that the patient has never had a convulsion or will never have one. The encephalogram, in addition to showing focal organic lesions, such as hematoma and scar formation, is of value when it shows an extensive pathologic condition which has obviously been present for a much longer time than the interval between the alleged trauma and the onset of the convulsions.

Since malingerers, particularly those attempting fraud, frequently repeat their performances in various hospitals, might it not be possible for all the hospitals in a given city to establish a central registry for cases of malingering and fraud? When a diagnosis of fraud or malingering was made, the patient's name and the pertinent data, together with a short abstract of the case, could be sent to this registry. The clerks of the court might also be induced to do likewise. It would then be a simple matter to get in touch with the registry, and I believe that the chronic offenders would soon be catalogued.

DR. FRANCIS M. FORSTER, Philadelphia: Dr. Hyslop's observations on the direct evidence of injury present an entirely new picture, and one which opens our eyes. Many of us are aware that in the early days of electroencephalography many errors were made and many abnormalities were recorded as generalized because the ears were connected electrically and used as a common ground. With further development it was found that the ears are active electrodes and are not grounds in the sense of radio grounds. Gibbs has shown a number of instances in which he and Bailey (*Tr. Am. Neurol.* **72**:180, 1947) removed sections of the temporal cortex and demonstrated by electroencephalograms that scars from mild injuries might have given rise to psychomotor seizures by producing discharging areas in the temporal lobe. I wonder whether Dr. Hyslop would comment on these innovations in the electroencephalogram which have given us better

results in recent years and whether he thinks that seizures might not subsequently develop in some of these patients.

Dr. George H. Hyslop, New York: As to the "ignored patient," I should not call him a malingerer. I agree with Dr. Scott that in these debatable cases one should not rely on either a positive or a negative electroencephalogram. A correct history speaks for itself. Dr. Scott spoke of seizures during the "acute concussion phase." The case of a patient who receives a concussion at 10 a. m., comes out of it at 10:05 and has a fit at 10:30 does not bear on the physiologic problem I attempted to discuss, that is, whether during the unconsciousness attributable to the concussion any epileptogenic zone may react. One does see patients who have recovered consciousness after mild concussional injury and who may have a seizure, one seizure, within a few minutes to an hour or two. I stated my experience as to the rarity of such instances.

I shall leave the discussion of a registry for malingerers to some other time—it would take too much time now.

As to the tendency to overlook things in clinics, referred to by Dr. Forster: I was in charge of a survey made eight or nine years ago of epileptic patients in the public school system of New York. We found only 1,000 acknowledged epileptic children among about 1,000,000 registered pupils, about half the expectancy. The hospital records made available to us were almost useless with respect to head injuries because of the lack of specific information as to the sort of injury which occurred. This sketchy sort of clinical recording is only too common, and it is utterly futile to take run of the mill hospital or clinic records and try to get any correlation between the injuries described in them and the fits requiring treatment.

As to "minor" head injuries leading to a pathologic process of the temporal lobe later, Dr. Forster was presumably referring to a reaction of the brain to injury greater than concussion. I do not think that the work of Gibbs and Bailey contributes much unless they have more facts as to the actual injuries that occurred in the persons they were dealing with. Sclerosis in the cornu ammonis in patients who had had seizures for years was described over twenty-five years ago.

Range of Psychoanalytic Therapy. Dr. C. P. Oberndorf, New York.

The dynamics of psychoanalytic psychology have become recognized as best adapted for interpretation and formulation of policy in a wide range of sociologic, penal, legal and educational movements, especially the ever expanding organizations for child care. As a therapeutic measure, the range of psychoanalysis has been extended to include a great variety of psychiatric conditions to which Freud had not originally considered it applicable, notably the schizophrenic and depressive syndromes and the so-called character neuroses. Because of this extension of the method, results which are completely favorable in the estimation of both patient and physician are not as numerous as might theoretically be expected. In recent years the tendency has been toward greater activity on the part of the therapist than was earlier considered desirable.

As yet, no unanimity of opinion has been established as to the type of case in which the response to psychoanalysis is most satisfactory, but in my opinion the best results have been obtained when the conflict manifested itself in physical conversion symptoms and when unproductive narcissism is weakened and redirected into productive, albeit narcissistic, endeavor.

The introduction of surgical procedures indicates that anxiety is very frequently relieved after severance of fibers leading from the cortex to the thalamus. In psychoanalysis one of the most important aims is to relieve anxiety through the

establishment of greater harmony within the ego. Inasmuch as anxiety can apparently be relieved by surgical means, it is not improbable that psychoanalytic procedures may be used in the future after mild surgical intervention which has diminished incapacitating anxiety.

DISCUSSION

DR. JOSEPH C. YASKIN, Philadelphia: It is gratifying to note that psychoanalysis is in many respects assuming a more realistic attitude toward the problem of treatment. When I returned from Vienna in 1928, I at once made up my mind that there is no need in the treatment of patients to spend five hours a week with them. Apparently in the course of years, other psychotherapists, much more qualified than I, have come to the same conclusion. In line with this, some of the pharmacologic modifications have been found to be of distinct benefit.

It is still somewhat a moot question where psychoanalytic therapy is of definite value. The so-called conversion hysterias are in the majority of cases amenable to any form of psychotherapy. In my own experience, the simpler the psychotherapy, the better is the result in the majority of cases. There can be no doubt that at present psychoanalysis in one of its several forms is the only method of treating severe psychoneuroses, notably anxiety hysteria and the compulsive-obsessive reactions. I am not so hopeful about the treatment of the constitutional psychopathic personalities. Distasteful as it may appear, one cannot escape the hereditary factor in most cases of this disorder; as an old judge told me many years ago, some of these persons are headed for the penitentiary no matter what anyone does for them. Some of the borderline conditions, both schizoid and affective, can undoubtedly be modified by prolonged psychotherapy. I have had all too little experience with the value of analytic therapy in true schizophrenic reactions. My impressions with the end results in these cases have not been favorable, and I sincerely hope that I am wrong, since other forms of treatment are equally disappointing. I have a conviction that the true manic-depressive reaction is not a psychologic disease. I have yet to see the prevention of recurrence of manic-depressive reactions by psychotherapy. I have seen a number of successful suicides during the course of analytic psychotherapy. Psychotherapy without shock therapy is of little value in the involution psychoses.

Like any other new discipline, psychoanalytic therapy is bound to overreach and become infested with parasitic concepts and formulations. It is hoped that in the course of time this discipline will reach a suitable place in the medical arts and sciences.

DR. C. P. OBERNDORF, New York: Dr. Yaskin has emphasized the difficulties and unsatisfactory results of psychoanalysis. I, too, have given considerable attention to this phase of psychoanalytic investigation, but with a different emphasis. Whatever criticism I have made of psychoanalytic procedure has been in the direction of attempting to improve the results and examine the shortcomings in psychoanalysis, without belittling what it has actually accomplished.

I think it is true that practically every psychotherapist now uses the profound knowledge of human nature which Freud formulated, a fact which is in itself evidence of the great value of psychoanalysis. When one says that no patient will require being seen five times a week, it is as much of a distortion as though one said that every patient need be seen only once a week. Patients differ not only in the fundamental conditions presented, but also in the type of psychotherapy needed. There may be cases in which a patient need be seen only twice or three times a week, but situations may occur when, for a time at least, the patient should be seen every day. It is a matter of choice how often one sees a patient, and in

this I dissent from the analyst who claims that unless a patient is seen five times a week the treatment is not a psychoanalysis. What one may accomplish is not necessarily measured by the number of times a week one sees the patient.

In conclusion, I should like to say that the pessimism which Dr. Yaskin has shown in regard to some of the obscure psychiatric situations, such as schizophrenia, is not entirely warranted. Certainly, psychoanalysis has been able to bring mental health to patients who were not benefited by any other approach. It is in the hope of increasing the applicability of psychoanalysis that I have investigated unfavorable results.

The new surgical procedures promise to clarify Freud's ideas that consciousness rests in the cortical region and that instinctive drives come from deeper anatomic levels. His therapeutic aim was always to reconcile unconscious drives with conscious strivings. It is not at all impossible that with increased knowledge of the pathways between instinct and consciousness revealed by psychosurgery it may be possible not only to localize anatomically the categories of the mind described by Freud but to make use of these findings therapeutically through the alleviation of anxiety.

Unilateral Prefrontal Lobotomy for the Relief of Somatic Pain. Dr. John E. Scarff, New York.

A series of 33 patients with unilateral prefrontal lobotomy performed for the relief of intractable somatic pain was reported. Sixty-six per cent of the patients were completely relieved of their pain; 18 per cent were partially relieved, and 15 per cent were not relieved. The follow-up period ranged from one to fourteen months. Careful psychometric and psychiatric appraisals were carried out before and after operation on a large percentage of the patients; these tests indicated that the operation had no adverse effect on intellect or personality. An unforeseen side effect of the operation was its facilitation in the termination of severe addiction to narcotics due to pain, without withdrawal symptoms. Typical cases were cited, and a statistical summary of results was given.

The operation is accompanied with little or no shock and can be performed on the most debilitated patient, when other types of operative intervention could not be tolerated. There have been no operative fatalities. The patient usually requires only five to seven days of hospitalization after operation.

DISCUSSION

Dr. Henry A. Shenkin, Philadelphia: The only disadvantage concerning this procedure is that perhaps it does not relieve pain permanently. In all the 14 cases in which Dr. Groff and I have had experience with unilateral lobotomy for the relief of pain the pain was relieved, at least temporarily. Contrary to our expectation that only the suffering would be relieved, actual relief from pain itself was produced. When the patients were questioned concerning their pain, at least in several recent cases that are fresh in my mind, they definitely stated that they had no pain. The problem whether these patients had their pain, but simply did not worry about it, is not entirely clear, at least in my experience. Of the 14 patients on whom we have operated, 5 had definite recurrence of pain—at six months, 1 at seven months, 1 at three weeks and 2 at three months. Three died within three months of the procedure, and operation on the remaining 6 patients was so recent that I do not think we can offer any satisfactory analysis of the results; the percentage of recurrence of pain, however, seems rather high. The mechanism of the relief of pain is not quite clear; consequently, the reasons for the return of pain

are necessarily obscure. If it is an interference with association pathways that gives relief, then perhaps the formation of new association pathways would account for the recurrence of pain. This, if true, would give little hope to those patients with nonfatal disease for whom we wish to obtain permanent relief from their pain.

We have sectioned the dominant hemisphere, as it seemed reasonable to believe that this would give the most certain relief from pain. It would be interesting, however, to hear some details on which hemisphere Dr. Scarff prefers to operate.

DR. JOHN E. SCARFF: I thank Dr. Shenkin for his thoughtful review of this paper and for his comments. It is interesting that his rate of satisfactory results is 63 per cent, while ours is 66 per cent, a rather close correlation. Why the results are unsatisfactory in 33 per cent remains a problem to be determined. One should not minimize even a five months' relief from pain.

I was recently at a meeting of neurosurgeons where they were bewailing the fact that their cures were only five year cures, but five year cures are accepted in other fields as "good" results. Neurosurgeons should take a more liberal attitude toward their results. If patients are relieved from pain for five to seven months, that is a fair accomplishment.

Dr. Yaskin has asked whether I have had any results in relief of trigeminal pain. I have not. I am anxiously awaiting such a case. I have had experience in 1 case of phantom limb which I described—that of the Greek general. I felt that part of his trouble was due to organic pain, but a large part of it was due to his sense of frustration; he had a useless arm, and he was resentful of that. I do not think that lobotomy will affect the emotional aspect of the phantom limb syndrome.

A Comparative Study of Antihistamine and Other Drugs in Parkinsonism. DR. PETER DENKER and (by invitation) DR. A. S. EFFRON, New York.

Diphenhydramine (benadryl®) has been found to be an effective drug in relieving the symptoms of parkinsonism in 76 per cent of a series of 46 cases. In 9 of 36 cases diphenhydramine and scopolamine in combination were more effective than either drug alone. Tripelennamine (pyribenzamine®) and thenylpyramine (histadyl®) were comparatively ineffective in treatment of parkinsonism in the great majority of cases. Mephenesin (tolserol®) likewise, when administered orally, was particularly ineffective. No appreciable improvement could be noted with the use of any of these drugs in 2 cases of hemifacial spasm, 3 cases of Huntington's chorea and 2 cases of spinal torticollis. It is important in all cases of parkinsonism to try the various drugs in both the atropine-scopolamine and the antihistamine series in order to find the ideal drug for each patient, as well as the dosage to suit his individual condition.

Hemorrhage into Hemangiomatous Cerebellar Cyst. DR. JOSEPH H. GLOBUS, New York.

In offering the case for consideration it is realized that it does not present any unusual clinical or anatomic features, such as those which have been encountered occasionally in neurologic practice. Indeed, some of the clinical manifestations in this case were apparently somewhat puzzling at first, and the sudden, almost precipitate, death of the patient on the second day in the hospital precluded a complete study and hence blocked a correct clinical diagnosis.

My aim in demonstrating the anatomic findings in the case is to draw a parallel between it and another case, in which autopsy revealed a similar condition. In the

second instance, however, another element was added, that of an alleged trauma to the head, which similarly was followed at the end of two days by sudden death.

PHILADELPHIA NEUROLOGICAL SOCIETY

Helena E. Riggs, M.D., *Presiding*

Regular Meeting, Oct. 7, 1949

Primary Neoplasms of the Third Ventricle. Dr. Elizabeth B. Eken (by invitation).

This discussion was concerned primarily with tumors originating in the third ventricle; these tumors constitute less than 1 per cent of the neoplasms found in the brain. The symptoms of these tumors and their relation to the surrounding anatomic structures were of major importance in the diagnosis.

Pressure is a major cause of the symptoms noted and produces such phenomena as the infundibular syndrome and thalamic responses. The commonest symptoms are headache, nausea and vomiting, papilledema, signs referable to the pyramidal tract and disturbances of coordination of exteroceptive and proprioceptive sense. Features particularly suggestive of lesions of the third ventricle are mildness and long duration of symptoms, relief of headache from postural change and the syncope related to postural change. Laboratory findings are of little significance, owing to the almost complete lack of positive signs and the difficulty of roentgenographic visualization.

A case was reported of tumor of the third ventricle from the neurologic service of Dr. A. M. Ornsteen, and the laboratory of neuropathology at the Philadelphia General Hospital. The diagnosis was a colloid tumor of the third ventricle, the patient having presented symptoms of twenty years' standing, resembling those previously discussed. The possible origin of these tumors from paraphysial rests or from epithelium was suggested.

Diagnosis should not be attempted on clinical findings alone, the difficulty being evident in the fact that the greater number are discovered at autopsy.

DISCUSSION

Dr. A. M. Ornsteen: A tumor of the third ventricle is not a problem of increased intracranial pressure alone. That is the final stage. It is the hope of the clinician to recognize this lesion by diagnostic methods in the presence of multiple and varied symptoms, which may in the early stages suggest a psychogenic condition, an organic process in the midbrain, encephalitis or a degenerative process, rather than a neoplasm.

Dr. Eken's report should stimulate thought along the line of correlation between organic and psychogenic symptoms, which may eventually be identified not as the result of structural disease, but perhaps as a transitory biochemical change in the cells of the gray matter of the diencephalon.

Dr. Joseph Yaskin: I saw this patient in conference. There was not much of significance at that time except that all agreed she probably had an intracranial lesion.

The course of a tumor of the third ventricle varies from case to case. It may be of many years' duration, as it was in this case, or it may be brief. I believe that at present the diagnosis is almost impossible without air studies. On the other hand, at the same conference, or at a conference thereafter, some good histories were presented, clearly describing the size and location of tumors in the third

ventricle. Perhaps Dr. Groff can tell us about some of his pleasant experiences with the operative intervention in these cases.

DR. ROBERT A. GROFF: This tumor is a challenge, not to the neurosurgeon but to the neurologist. It behooves the latter to think of a tumor of the third ventricle and to ask us surgeons to determine whether or not it is such a lesion. We can demonstrate a tumor in this region very easily by air studies.

I have seen a number of these tumors and in certain instances have had good results with the complete removal of the neoplasm. The cyst is, of course, the most favorable type of lesion, and one can handle it more readily surgically, collapsing and removing it through the foramen of Monro.

DR. ELIZABETH B. EKEN: Perhaps I should say that a review of the literature showed that a very large percentage of tumors were found at autopsy; perhaps my paper was influenced by the finding of this tumor at autopsy after so long a period. I neglected to state that Dr. Dandy, in his monograph, dealt very largely with the neurosurgical removal of these tumors, and with their successful removal.

Substratum of Manifestations of Syphilis in the Central Nervous System. DRS. GEORGE WILSON, CHARLES RUPP, HELENA E. RIGGS, WILLIAM W. WILSON and HAL PITMAN (by invitation).

Of a series of 339 cases with serologic or pathologic evidence of syphilis, indisputable histopathologic evidence of involvement of the central nervous system was present in only 105 (31 per cent). In 29 of these 105 cases, however, the accompanying nonsyphilitic pathologic changes must be considered an equipotential etiologic factor. In an additional 71 cases symptoms referable to the central nervous system might be accounted for on the basis of existent syphilitic cardiovascular disease, in spite of the absence of syphilitic involvement of the nervous system. Syphilis, therefore, may be incriminated as a possible factor in 176 cases (52 per cent). In the remaining 163 cases pathologic study suggested nonsyphilitic disease as the predominant cause, and syphilis was incidental, rather than primary, with respect to nervous and mental symptoms.

Extreme caution, therefore, must be exercised in concluding that neurologic manifestations in a patient with positive serologic reactions are due to syphilis alone. The possibility that nonsyphilitic pathologic changes may be equally or entirely responsible must always be borne in mind. From the point of view of practical clinical management, positive serologic reactions should not justify the abandonment of further diagnostic studies which may more positively delineate other causes.

Adequate antisyphilitic treatment should be mandatory. It must be recognized that therapeutic failure may result from lack of critical evaluation of nonsyphilitic etiologic factors. Supplemental treatment directed toward the nonsyphilitic disease is also indicated, even in the presence of syphilis of the central nervous system.

DISCUSSION

DR. GEORGE D. GAMMON: Dr. Wilson and his co-workers have done us a service in calling attention to the fact that the establishment of the diagnosis of syphilis does not mean that the infection is responsible for the symptoms at hand. I have been interested in cases without a history of syphilis, a negative Wassermann reaction of the blood, a positive reaction of the spinal fluid to the Kolmer test and neurologic disease which does not resemble neurosyphilis. One such case was that of pathologically acute multiple sclerosis.

DR. HELENA E. RIGGS: Dr. Rose, when he was at Philadelphia General Hospital, made an adjustment in the Wassermann test of the spinal fluid. He pointed out that the Wassermann reaction is adjusted for the protein content of blood, which is much higher than that of spinal fluid. In evaluating the positive Wassermann reactions of the spinal fluid, one must consider the amount of protein present and the possibility of false positive reactions due to a low protein content. Possibly for four years the Wassermann tests of the spinal fluid at Philadelphia General Hospital have been adjusted by use of egg albumin.

DR. WILLIAM W. WILSON: In a future paper, we intend making an analysis of cases with positive and those with negative serologic reactions. There are many cases in which a diagnosis of dementia paralytica is made on the basis of a positive serologic reaction of the blood or the spinal fluid, and the condition is diagnosed as such no matter what the mental symptoms are.

Primary Neoplasms of the Central Nervous System in Domestic Animals.
DR. H. M. MARTIN (by invitation) and DR. JOHN T. MCGRATH (by invitation).

The incidence of primary neoplasms in the central nervous system of domestic animals is reportedly very low. In a series of 2,898 autopsies performed at the University of Pennsylvania School of Veterinary Medicine, 9 such tumors were encountered, an incidence of 0.3 per cent. During the past eight months we have attempted to examine the brains of all dogs and cats necropsied. In this period 337 autopsies were performed, and 5 primary intracranial neoplasms were found, an incidence of 1.5 per cent. In the same series 27 animals had malignant neoplasms, 3 of which showed metastasis to the brain.

Multiple meningiomas were noted in 2 cats. In both cases the largest growth apparently had its origin in the tela choroidea of the third ventricle. An extramedullary malignant meningioma was observed in the lumbar region of a dog.

Four gliomas were presented: 2 fibrillary astrocytomas in dogs, an ependymoma in the midbrain of a mule and a dedifferentiating ependymoma in the cerebrum of a dog.

A hematoma of the gasserian ganglion and an arteriovenous angioma were also observed in dogs.

DISCUSSION

DR. H. M. MARTIN: As indicated in our paper, cerebral neoplasms do not seem as rare as the literature would suggest. Both primary and secondary neoplasms occur in the central nervous system of domestic animals, in many instances without clinical symptoms. We have had examples of secondary melanoma, hemangioendothelioma, adenocarcinoma, etc., in the brain substance, noted only on routine examination. Cholesteatoma of the choroid plexuses is common in equine animals. These may attain the size of a hen's egg. These animals frequently present signs of internal hydrocephalus.

In addition to tumors of the central nervous system, we also find other pathologic changes in the central nervous system, all of which are of common interest to neuropathologists in both the medical and the veterinary field.

DR. JAMES J. RYAN: I should like to ask Dr. Martin and Dr. McGrath whether they ever encountered medulloblastoma in animals.

DR. FREDERICK H. LEAVITT: Dr. Riggs tells me it was four years ago that she and I reported a clinicopathologic study on a monkey in the hospital of the School of Veterinary Medicine the behavior of which was distinctly psychotic and

antisocial and partook very much of the pattern of patients whom one sees in the psychopathic ward at the Philadelphia General Hospital.

DR. HELENA E. RIGGS: There were widespread changes in the brain of the animal Dr. Leavitt mentions, as well as damage to the heart muscle, as I remember.

DR. JOHN T. MCGRATH: In answer to Dr. Ryan, I was fortunate enough to examine the collection of brain tumors in animals at the Army Institute of Pathology, Washington, D. C. Among the collection was a medulloblastoma of the cerebellum of a cow. There were also 2 acoustic neuromas from cattle. A doctor there from the Cornell School of Veterinary Medicine stated that he frequently found oligodendromas, and I believe he said that Dr. Bailey had looked at a number of his tumors, including glioblastoma multiforme.

Rudolph Jaeger, M.D., *Presiding*

Regular Meeting, Nov. 4, 1949

Arteriovenous Aneurysm of the Brain Cured by Ligation of the Left Middle Cerebral Artery: Report of a Case. DR. RUDOLPH JAEGER.

A woman aged 23 vomited and suddenly became comatose, with right hemiparesis and complete motor aphasia. The bloody spinal fluid with stiffness of the neck and legs suggested a ruptured aneurysm. Arteriographic examination demonstrated an arteriovenous aneurysm of the left motor area. Craniotomy revealed a subcortical clot, 2.5 inches (7.5 cm.) in diameter, back of the sylvian fissure and many huge cortical veins with swirling arterial blood and a palpable thrill. The clot was evacuated, and a silver clip was placed on the middle cerebral artery 3 mm. beyond the division of the internal carotid artery into the anterior and middle cerebral arteries. The phenomena referable to the arteriovenous fistula immediately disappeared, and the patient recovered rapidly to the point where at the time of this report, nine months after operation, almost complete speech and muscular strength have returned. It is probable that ligation of the left middle cerebral artery is usually fatal when there is no arteriovenous communication. If not fatal, it will certainly produce permanent hemiplegia and loss of speech in a right-handed person. The long-standing presence of a congenital arteriovenous aneursym in this case stimulated growth of collateral arterial supplies in such abundance that ligation of the middle cerebral artery was considered safe. The operative cure justifies this conclusion.

DISCUSSION

DR. MICHAEL SCOTT: I have a patient with a similar condition, but in her case the lesion is so large that I do not dare to touch it. I have had experience with ligating the middle cerebral artery in 2 patients, and both survived. In each patient, however, the artery supplied the nondominant hemisphere. Each patient had complete paralysis of the arm and partial paralysis of the lower extremity after the ligation.

DR. ROBERT A. GROFF: It it true that these lesions are not entirely hopeless but can be cured by surgical intervention in many instances. Dr. Jaeger ligated the middle cerebral artery in the present case. This may not be necessary in the case of other lesions for Dr. Olivecrona reported on a number of cases in which he had excellent results without ligation and stated that it is far better to operate on the aneurysm after a hemorrhage, because the clot compresses the vessels and gives one room to work.

Recently, Dr. Ernest Sachs, of New Haven, advocated the use of slow coagulation of the vessels in order to shrink them and thus permit clipping. In this way a minimum amount of vascular supply to the brain is destroyed.

I now have a case in which an arteriovenous anomaly of the parieto-occipital area has caused three episodes of bleeding. The last one precipitated hemiparesis, which has very nearly cleared. It is because I fear a hemiplegia that I hesitate to attack the lesion surgically.

DR. RUDOLPH JAEGER: I had ligated a middle cerebral artery once before, and the patient died. Perhaps as more is known about the circulation through the middle cerebral artery, one will feel freer to ligate this vessel.

DR. HENRY WYCIS: The problem of ligating cerebral arteries is an interesting one. Dandy reported that ligation of the left anterior cerebral artery produced loss of consciousness, but Poppen reported 10 cases in which ligation did not produce loss of consciousness unless it was done at a time when the patient was in shock and the blood pressure low. Apparently, when collateral circulation is sufficient, ligation is not necessarily disastrous.

Neuropathologic Changes in Nitrogen Trichloride Intoxication of Dogs.
DR. F. H. LEWEY.

Nitrogen trichloride (agene®) is the agent used in most wheat-consuming countries to bleach and soften the yellow wheat flour, which is hard to bake. This substance has been found to be toxic to dogs, rabbits and ferrets but not to monkey, cat, guinea pig and man. Dogs fed a diet rich in nitrogen trichloride become ataxic within a few days and have running fits. Electroencephalographic records of these dogs suggest an epileptoid condition. The pathologic changes in the central nervous system are characterized by patchy liquefaction necrosis in the deep layers of the cerebral cortex and of the U fibers, extending slightly into the white matter. These changes are diffusely distributed over the cortex but are most pronounced in the hippocampus. Severe changes of a different character are to be seen in the cerebellum, specifically in the Purkinje cells, in their afferent and efferent fibers and in the interconnecting system of the basket cells and their axis-cylinders. Milder alterations occur in the nerve cells of the dentate and the roof nuclei. The drug has in the meantime been withdrawn from the market and replaced by chlorine dioxide, which is harmless even for dogs.

DISCUSSION

DR. MATTHEW MOORE: Could the apparent specificity of this substance for the cytoplasm of nerve cells in certain species be explained by differences in metabolism? Is it possible that in the human being the substance is metabolized before it reaches the nervous system?

DR. F. H. LEWEY: I can offer no complete explanation for this specificity. There are many examples of such specificities, however. Poliomyelitis and probably syphilis are predominantly human diseases. Many toxins also show a predilection for certain species.

High Cervical Lesions Simulating Multiple Sclerosis and Syringomyelia.
DR. TEMPLE FAY and DR. FRANK F. WILDEBUSH (by invitation).

The diagnosis of multiple sclerosis is becoming increasingly frequent. Some authorities (Grinker, R. R., and Bucy, P. C.: Neurology, ed 4, Springfield, Ill., Charles C Thomas, Publisher, 1949) rate it third in frequency among neurologic disorders.

In 21 cases with chronic progressive symptoms and classified for many years by recognized authorities as instances of multiple sclerosis focal signs eventually developed which warranted exploratory laminectomy of the high cervical area. The pathologic picture encountered consisted of one or more of the following conditions:

1. Anterior subluxation of the atlas, similar to that recognized in platybasia or that of post-traumatic origin (severe fall on the buttocks, striking the top of the head or sudden pressure of the head on the upper part of the spine, sudden snapping of the head backward, breech presentation, etc.).

2. Focal areas of opalescent subarachnoid fibrosis and adhesions to the arachnoid, the spinal roots, the cord and the vessels (traumatic histories predominating).

3. Collections of clear spinal fluid in sealed-off cavities situated between the dura and the arachnoid and associated with adhesions to the arachnoid, the spinal roots, the cord and the vessels (traumatic histories predominating).

In some of the cases formerly considered as typical cases of multiple sclerosis reexamination was made in the light of the lesions disclosed in the cervical portion of the cord. In 4 cases the symptoms and typical findings were sufficient to justify the diagnosis of true multiple sclerosis; in 1 case operation was performed, without relief, and in 7 there was evidence of focal lesions in the high cervical area, often with verification at operation. In 10 other cases bearing the diagnosis of multiple sclerosis which had repeatedly been confirmed by competent authorities high cervical lesions were recognized and operation revealed focal compression by the atlas or circumscribed subarachnoid fibrosis. In 4 cases a condition diagnosed as syringomyelia proved to be compression by the atlas with adhesions.

So striking has been the similarity of symptoms of certain high cervical lesions and multiple sclerosis that review of all cases of so-called multiple sclerosis is indicated.

Dr. Wildebush demonstrated 4 cases in which decompression of the high cervical region had been followed by definite improvement, in spite of the fact that in all of them a diagnosis of multiple sclerosis, syringomyelia or syringobulbia had previously been made.

DISCUSSION

Dr. Michael Scott: I agree entirely that it is important to look for remediable lesions instead of simply theorizing about a possible pathologic condition. For example, many neurosurgeons now realize that they failed to recognize herniations of the nucleus pulposus in cases of sciatica before there was the present awareness of the significance of this lesion. In the study of obscure lesions in the high cervical regions, myelography is undoubtedly justified, and I, too, feel that it is better, if the studies so indicate, to explore than to be content to make the diagnosis of a hopeless disease.

Dr. Henry Wycis: Dr. Fay's warning should certainly be heeded. It is important to emphasize that his approach to this problem led to a better understanding of the clinical significance of platybasia. This deformity had been described by the German investigators as an anatomic curiosity, and it was only after he had operated in the 3 cases reported by W. L. Chamberlain (*Yale J. Biol. & Med.* **11**: 487 [May] 1939) that other surgeons began to attack this condition surgically, with some success. He deserves full credit for stimulating this interest.

Dr. Walter G. Scheuerman: At the Graduate Hospital we have a somewhat different feeling about the pathologic process in these cases in which the symptoms simulate degenerative diseases of the spinal cord. We now have a series of 20

cases, in all of which cervical myelograms showed evidence of either a block or a defect in the cervical region. Operation revealed midline herniated cervical disk, usually between the fifth and the sixth cervical vertebra, less often between the fourth and the fifth cervical vertebra. The disks were not removed because of their position; however, the dentate ligament on each side of the cord was cut so as completely to decompress the cord. The patients have shown some improvement in the spastic gait, but in our experience the neurologic signs have remained the same.

I should like to ask Dr. Fay whether a myelogram was performed in any of his cases and to what extent the laminectomy was carried out.

DR. RUDOLPH JAEGER: It has long been recognized that pathologic involvement of the structures surrounding the spinal cord and meninges will produce disease in the enclosed soft tissue. It was von Bergmann who emphasized this point in the relation of spinal arthritis to chronic myelitis, and I have not noted that the cervical region was more frequently involved than other parts of the spinal canal. In my own experience, I have not been impressed with the results of laminectomy in the management of these secondary soft tissue reactions. I am interested in the theory of the water hammer effect of accumulations of fluid against the cord, and I feel that it would be hard to prove this point of view. Does Dr. Fay know of any definite proof that such an effect occurs?

All have made mistakes in the diagnosis of disease of the spinal cord. I am sure that every one tries to avoid such errors by using ethyl iodophenylundecylate (pantopaque®) myelography whenever there is any real doubt about the diagnosis.

I am not clear about the criteria which were used for operating on these particular patients.

DR. ARNOLD LEVINE: I am much interested in the possible significance of arachnoidal thickening. In 1942 I had occasion to review this subject in detail, and I was left with the impression that it was difficult to be sure whether the arachnoidal thickening was primary or whether it was secondary to changes which had started in the cord itself.

DR. TEMPLE FAY: Ethyl iodophenylundecylate does not always show obstruction in the cervical canal. Laminectomy with decompression gives symptomatic improvement, chiefly owing to better local circulation in the cord and probable relief of ischemia.

In my opinion, it is unwise to make a diagnosis of multiple sclerosis in cases in which mental deterioration with ocular signs and speech involvement is not manifest and the disease has not progressed over a period of years to manifestations of diffuse cerebral involvement. I feel that if focal signs appear and the disease process stops at the high cervical level exploratory laminectomy is justified and the condition is not true multiple sclerosis.

I believe that release of the constricting adhesions permits improvement in intrinsic circulation to the cord itself. This, in turn, permits better function and improvement in symptoms.

Helena E. Riggs, M.D., *Presiding*

Special Meeting, Nov. 29, 1949

Cerebral Localization in Aphasia and Agnosia. DR. J. M. NIELSEN, Los Angeles.

It gives me great pleasure to speak in Philadelphia on my favorite pastime, the study of aphasia. I confess to you that the first edition of my little book

was prompted by an emotional upheaval on seeing Dr. Charles K. Mills's money spent for research on localization in aphasia with results which denied the correctness of his views. I resolved then and there to write up the results of my own experiences corroborating Hughlings Jackson, Mills and Henschen, since, after all, Mills was right.

Confining my comments to a presentation of slides and their elucidation, let me say in summary that when one can duplicate the motor speech defect of hemispherectomy by a small lesion in Broca's convolution (about 40 cases on record) and the auditory verbal agnosia resulting from hemispherectomy by a small lesion in the cortex of Wernicke's area, one must have found the areas in the hemisphere essential to motor and sensory speech. Similarly, when it was proved that a lesion of the major angular gyrus caused alexia with agraphia, whereas a subcortical lesion of that gyrus caused alexia without agraphia, it was clear that engrams of recognition and recall of written symbols were located in the cortex of the angular gyrus.

In addition, we have studied visual agnosia for objects, a more fundamental defect than that of aphasia. It was found that various persons lay down engrams in infancy in different places. Some have all in one occipital lobe; others divide them between the two, whereas still others lay all down on each side and can lose either lobe without having any defect. The slides will demonstrate these points and show that recovery, when it occurs, is through function of the other hemisphere.

DISCUSSION

DR. JOSEPH YASKIN: I should like to report briefly a case of alexia in a child. A girl aged 7 years had no difficulty with her reading, spelling and writing at the end of her school term. When she returned in the fall of the same year, she experienced difficulty in all these functions. Neurologically, she was completely normal. A detailed study by one of our best neurologists failed to disclose any disturbances in the central or peripheral fields. All I could find was inability to write on dictation or copying and some difficulty in reading. She had no nephritis, endocarditis or source of embolism, and I was unable to answer the question whether the condition was an emotional problem in a 7 year old, second grade child or the beginning of a neoplasm that I was unable to detect.

DR. KATHERINE MCBRIDE (by invitation): Dr. Weisenburg and I worked on a series of aphasic patients from 1929 to 1934, the year of his death. We had some pathologic material, but no material as regular or extensive as Dr. Nielsen has indicated. My particular interest was in the psychologic studies. As Dr. Nielsen was speaking, I began to think that we were a little confused here on the East Coast because even when we had aphasia it was not so clearcut! More seriously, that is partly a matter of approach; we were interested in the psychologic characteristics. It is partly a matter of degree. For example, Dr. Nielsen has outlined three possible types of visual agnosia. He has differentiated these categories for the patients he has had. Others, however, might require a fourth or a fifth type; so even here one has some picture of the complexity which close studies of language and behavior show.

One of the problems in aphasia that struck us as most difficult was that of assessing the language disturbance in relation to the patient's earlier ability to speak or to think clearly. When we were dealing with relatively uneducated patients, we sometimes got very different evidence of loss than we did with some of the patients with high grade intellectual development. Our impression of the aphasia in all of them was, as I suggested, not the clearcut picture Dr. Nielsen has shown.

DR. N. W. WINKELMAN: At the time that Dr. McBride and Dr. Weisenburg were working on aphasia, the neuropathologic laboratory at the Philadelphia General Hospital, which I directed then, was used extensively. Unfortunately, most of the autopsy cases were not as well catalogued as the cases shown here.

One case was corroborative of a group reported here. A man was admitted because of complete motor aphasia. He was discharged after a few months without improvement. He returned to the hospital five years later with erysipelas and died. His speech had been normal for two or three years. At autopsy softening of Broca's entire area was seen.

We rarely saw the type of lesion that Dr. Nielsen has shown, especially in the occipital region. He has been fortunate to have studied the patients clinically and then to have had the opportunity to correlate his clinical observations with the pathologic picture.

DR. F. H. LEWEY: Dr. Nielsen has the great advantage of working with a material consisting of vascular lesions, whereas the material to which Dr. McBride referred was mainly tumor material. In addition, Dr. McBride, in her work with Dr. Weisenburg, was primarily interested in the psychologic aspect of aphasia, whereas Dr. Nielsen, for good reasons, has concentrated his research on the organic side of the problem and on the attempt to localize the lesions. Both approaches to the problem of aphasia are legitimate and necessary, but their results are not comparable.

DR. FARNCIS C. GRANT: I do not believe that the neurosurgeons can clarify or improve on the material that Dr. Nielsen has produced. Dr. Lewey's point is extremely well taken. A brain tumor is an expanding, changing type of lesion. After complete or incomplete removal of the tumor, the area which has been affected by the growth has a chance to recover. Consequently, the neurologic damage caused by such a lesion is not as definite or as cleancut as the vascular lesions that Dr. Nielsen showed.

I have seen cases in which there is definite support for Dr. Nielsen's claim that the right side of the brain will take over so far as speech is concerned. Dr. Groff and I have a fifteen and a nine year period of survival in 2 cases in which the entire left temporal lobe was excised to the extent that, after excision, the edge of the incisura medially and the optic nerve anteriorly were readily seen. These 2 patients, whom I have seen within the last year, are making their way readily in business and did not have any difficulty with speech. One of them has a stutter, if he becomes irritated, but he has a complete and perfect choice of words. The patient whose survival period is fifteen years was sent, six years after the operation, to the psychologic clinic at the University of Pennsylvania to see whether he had any difficulties in the selection of words, in their use in their proper context or in similar tests. So far as could be determined, for his age and general education, he had an 85 per cent record, which is better than average.

I have no doubt that with removal of the speech center on one side the nondominant hemisphere will take over. Dr. Nielsen may say that we are talking about the temporal lobe only, and not the frontal lobe, and that we have not really destroyed Broca's area. Certainly, we were far enough back to involve the language formation center, of which Dr. Nielsen spoke. Consequently, with the dominant hemisphere ablated, the contralateral hemisphere, given time, experience and training, will function equally well. Moreover, it is very difficult, after the opposite side has taken over, to show that there is any loss of the ability to speak, and to speak accurately.

DR. CHARLES RUPP: Can Dr. Nielsen give any statistics on the percentage of patients who spontaneously recover their speech function by the other side's taking over without special training?

DR. GABRIEL SCHWARTZ: Has Dr. Nielsen seen any case or cases in which there were bilateral, identically located lesions which disturbed the function of language, and in such cases was any recovery of function noted afterward?

I know that Dr. Nielsen says there is no such thing as sensory apraxia. It seems to me that in a case of tactile agnosia the person cannot handle objects well and will drop objects with the eyes closed. The skilful handling of objects is lost. Could this be considered a form of apraxia, due to impairment on the sensory side?

DR. SHERMAN GILPIN JR.: It might be worth while for Dr. Nielsen to say a word about the differentiation between the psychotic and the partially aphasic person, since frequently the latter is admitted to a department for psychopathic patients or to a general hospital and is considered insane.

DR. J. M. NIELSEN: On the basis of Dr. Yaskin's review of his case, I am unable to determine the pathologic nature of the lesion.

Dr. McBride asks about psychologic factors. I acknowledge their importance but had to omit mention of them for lack of time. They should be given full consideration in any case studied.

Dr. Grant raised the question of aphasia in cases of cerebral tumor. One cannot study localization in aphasia on the basis of expanding lesions because of pressure phenomena and because the autopsy findings do not represent the condition at the time of the clinical study. Neurosurgery, however, has greatly contributed to knowledge of aphasia by giving known discrete lesions after the operation.

As to sensory apraxia, I can only say that by definition apraxia is a motor phenomenon.

Book Reviews

Studies in Lobotomy. By Milton Greenblatt, Robert Arnot and Harry C. Solomon, Editors. Price not given. Pp. 495 with many tables and charts. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1950.

Many contributions on lobotomy have already come from the Boston Psychopathic Hospital; some of them are found to be reprinted or amplified in this volume, but many contributions that have not heretofore appeared in print are also presented. From a total of more than 500 cases, 205 of the earlier ones were selected for particularly careful evaluation on the basis of a long follow-up period of observation. The editors state: "As to the selection of patients most suited for lobotomy, elaborate studies correlated 83 different preoperative factors with eventual clinical outcome. Only a few factors have striking predictive value. A history of a rapid onset, absence of auditory hallucinations, and presence of insight greatly favored a good outcome after operation; the most favorable diagnostic label was either psychoneurosis or affective disorder. . . . Patients who possessed a syndrome including fear, worry, depression and tension ("tortured self-concern") were likely to be improved by operation whatever the diagnostic category."

As for results, some 40 per cent of chronically ill hospitalized patients were able to live at home, and half of these were found to be self supporting. A high proportion of those remaining in institutions lived a more satisfying and contented existence. "These conclusions lead us to continue the operative procedure with the belief that we are adding to the total joy of living and, at the same time, we are affording the opportunity for studies relating to an understanding of brain and frontal lobe physiology, and to the mechanisms and dynamisms of the psychoses and of mental stress."

Members of the staff of the Boston Psychopathic Hospital contribute chapters on various aspects of lobotomy, ranging from the surgical technic through anatomical and physiological studies, electroencephalography, skin temperature, vesical function, pain reaction, and so on, to psychometric, sociometric and occupational therapy adjustments and rehabilitation. The effectiveness of these chapters is variable; some are cameo-like in their clarity, whereas others are a bit like putty. The bibliography abounds in erratic spelling of names. The meat of the work is in the one to four year follow-up study of the 205 cases, but even this number is not enough, considering the variety of cases, particularly the deteriorated ones, and the variability of the operative incisions.

Some paradoxical findings are encountered. Whereas many patients become incontinent after operation, a respectable number that wet themselves before operation cease to do so. Epileptic attacks develop in some 10 per cent of patients operated on (mostly in those who have undergone a long series of shock treatment), but some patients are apparently relieved of convulsive tendencies. Some patients are relieved of alcoholism, and some are precipitated into it, by lobotomy. Some patients do better during rehabilitation on a total push regimen, whereas others improve more rapidly if left to their own direction. The prime paradox is the increased reaction to painful stimuli observed after lobotomy, together with the complete relief of intractable pain in cases of cancer and other distressing diseases. It is just these variations and paradoxes that make this volume of studies worth

while. Some questions are answered, but for every question answered, a dozen seem to spring up to keep the student of psychosurgery on the alert.

The volume is a solid, rather sober one, crammed with facts and illuminated with many tables. On the other hand, there is little theorizing, and the arguments pro and con are held on a rather practical, possibly materialistic basis. In the introduction, Solomon writes: "The viewpoint of others seemed to be more distinctly emotional, based upon a conscious or unconscious belief that the frontal portion of the brain is a holy of holies, or upon some archaic thoughts concerning the brain as the seat of the soul." The fact that lobotomy was undertaken only in 1943, seven years after publication of the monograph by Egas Moniz, and that there had already accumulated a considerable body of experience with the method in this country, is an indication of the conservatism with which lobotomy was undertaken. It is fortunate that Solomon and his co-workers have carried through such a major project and have issued such a well documented report of their studies.

Pre-Frontal Leucotomy: A Survey of 300 Cases Personally Followed over 1½-3 Years. By Maurice Partridge, M.D. Price, $7.50. Pp. 496. Basil Blackwell & Mott, Ltd., 49 Broad St., Oxford, England, 1950.

Experience with prefrontal leukotomy was fairly well advanced in England when the author started on his problem of following up 300 patients who had all been operated on by the same surgeon, Mr. Wylie McKissock. He tracked them down with unremitting zeal from John O'Groats to Lands End, and even overseas to France and South Africa. Having known these patients before operation, and having studied their case records with intimate care, he was able to assess the changes that had taken place in them at intervals of six months, one year, two years and three years after operation. He brings to this study not only a good grasp of psychiatric principles and certain useful psychometric tests, but also a wealth of direct quotations from patients and their relatives that establish the personality alterations in convincing fashion. The work is done with the consummate skill of a student of classics unhampered by the rigidity of the academic atmosphere. His patients are people, with hearts and souls to be tormented before operation, and friends and relatives to be tormented (but only at times) after operation. A rich, running prose that achieves effect often through understatement is rather characteristic of this British author.

The 300 patients are divided along the conventional lines of psychiatric nosology and then subdivided into small and smaller groups, until in some instances there are only three to a group. There is only one table (dealing with the schizophrenic cases), although similar tables for other groups might have made for easier comparison, one with another. The outstanding fact emerges, however, that the more emotional reaction there is in the malady, the better the eventual result. Patients with fixed delusions, fixed hallucinations, fixed depressions, fixed compulsions, fixed anything, do not come out as well as do those with alterations in symptoms. Experience with a few cases of psychopathic personality, of alcoholism and drug addiction and of organic brain disease would serve to deter the enthusiast from expecting too much of leukotomy.

This is essentially a social study, a medically tinged set of observations on patients in their homes and at work, at play and at meals, when they are enjoying themselves and when they are faced with disagreeable tasks. Indolence, procrastination and outspokenness are the principal personality alterations that can be attributed to operation. There is slightly less evidence for actual intellectual

deficit, although the author likes the reversal of digits and serial subtractions as means of eliciting such deficits. He finds on the whole that patients are less creative, less interested in their environments, less in need of friendship, of stimulation, less marked in their enthusiasms and more prone to be satisfied with trivialities. "The total pattern of reaction is simpler, marked by an essential tendency towards avoiding discomfort and courting pleasure, with lowered standards of criticism, reduced self-awareness, and diminished self-control, which last is considerably offset by the lessening of responsiveness in general."

Partridge continues: "Yet, though we hesitate to impose this reduction upon the patient, it is one which is often recommended by physicians, and wisely, for it amounts to little more than the oft-given advice to take more relaxation, to make fewer demands upon and to live essentially within the limitations of the self. The difference is that postoperatively the patient has no option, nor the same potentialities.

"But the post-operative state should never be judged except in the light of the pre-operative condition and the prognosis which that carried. If this summary of the post-operative personality seems gloomy, it must be remembered that all the patients in this series were severely ill, that many (if not most) were hopeless chronic invalids, and many were very poor material."

Among the 300 cases, there were 10 operative and postoperative deaths. Thirty patients suffered convulsive seizures, most of them controlled by medication. Urinary incontinence substantially cleared up within six months, and only three patients were troubled by persistent wetting. Other complications were unimportant, with the possible exception of overeating.

The author permits himself some speculations, which are included in a final chapter, entitled "Parturient montes. . .," in which the hypothalamus comes into its own. To quote from the author again: "It would seem reasonable, therefore, to suppose that it is at levels below the thalamus that the sources of primary mood disturbances are located, and that it is at levels above the thalamus that these disturbances are increased by elaboration." This is by no means all, but will reveal a trend in the thinking of the author which lends a certain plausibility to his ideas, which he admits "have touched but the fringes of the subject."

News and Comment

NEW INSTITUTE FOR NEUROLOGICAL RESEARCH IN WESTERN GERMANY

The Otfrid Foerster Institute for Neurological Research recently was opened in Detmold, Germany. The director is Dr. F. W. Kroll, one of Dr. Foerster's students in Breslau. The institute will carry on some of Dr. Foerster's more recent investigations.